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THE HORSE SERUM (FOREIGN PROTEIN) TREATMENT OF PYELITIS AND PYURIA*

DAVID MURRAY COWIE, M.D.

ANN ARBOR, MICH.

Until recently we have been unable to determine definitely whether a given case of pyuria is one of pyelitis, cystitis, or pyelocystitis. Common custom has been to designate all cases presenting the more or less characteristic symptoms when associated with a definite excess of leukocytes in the uncentrifugated urine or definite pus in the sediment pyelitis. Particularly was this diagnosis considered very probable if the urine was acid and colon bacilli were found in smear and on culture. It is only possible, however, to diagnose pyelitis definitely by means of the cystoscope which enables one to differentiate the portion of the reno-vesical system from which the pus is coming. It is possible to demonstrate this by means of kidney massage and a certain technic which I described fifteen years ago,[1] but the cystoscopic method is by far the best method and instruments are now made small enough to pass into an infant's bladder and permit of ureteral catheterization.

Some clinicians have gone so far as to assert that unless the colon bacillus is found we are not dealing with a pyelitis. This opinion, however, is held now by but a few. A case recently observed in a young woman, aged 20, with pyuria of three years' standing illustrates this point very well. The urine was heavy with pus, the stained specimen showed pure culture of a coccus; specimen from the right ureter showed the same, and culture proved the coccus to be *Staphylococcus pyogenes albus*. The urine was at all times distinctly acid, which is not the rule with this type of infection. The *Staphylococcus albus* splits urea, rendering the urine alkaline, but it has failed to do so in this case and no organisms were associated with it that would ferment sugars. Case 8 also illustrates this point and it is interesting to note a double infection in this patient. The colon bacillus was recovered from the right ureter, the *Staphylococcus albus* from the left.

* Received for publication, May 25, 1922.

* From the Department of Pediatrics and Infectious Diseases, University Hospital.

1. Cowie: Am. Med. **11**:36, 1907.

Nor can we determine a pyelitis by the symptom of pain in the flank, below the costal margin or in the kidney region, even when it is associated with fever and pyuria. I have recently seen a case of pyuria in a woman, aged 56, with pain in the right kidney region, pyuria, colon bacillus on culture, and acid urine. On cystoscopic examination an infected bladder was found and clear urine from both ureters. There were no classical vesical symptoms in this case. Pyelograms showed the kidneys to be normal in shape, etc. These cases serve to show that symptoms characteristic of pyelitis, even distinct pain in the kidney region, may not be due to pyelitis; that pyelitis may definitely be present and the affected kidney deliver acid urine containing the *Staphylococcus albus*.

My experience deals with the treatment of a number of cases of pyuria, some of which are doubtless cases of pyelitis by the older standards, but only two of which have been proved to be pyelitis by cystoscopic examination. The cystoscopic examinations were made by Dr. Hugh Cabot.

A case (1) of pyuria of long standing in a girl, aged 10, came for treatment Jan. 21, 1916, while I was studying the effect of Bier's hyperemic stasis in arthritis. Having had difficulty in clearing up cases of pyelitis in infants and young children by the usual methods, it occurred to me that if we could induce a hyperemia of the kidneys an infected pelvis might be cured. It is a well known fact that horse serum brings about a hyperemia of the skin and joints and might induce a hyperemia of some of the internal organs. I decided to induce hyperallergy in this patient with horse serum, and then produce an immediate reaction at will with the idea that during the reaction the kidneys might become engorged with blood and a result similar to that which occurs in arthritis after hyperemic stasis be produced. I did this and was interested to find that the pus disappeared from the urine completely after the third subcutaneous injection with no recurrence to the present time.

However, I am not at all convinced that my reasoning as to the explanation for this is correct. Since this time, much knowledge has accumulated on the action of foreign protein in infectious processes in general. The bulk of evidence would appear to support the idea that the beneficial effects obtained in treating pyuria with horse serum come from the nonspecific action of the protein itself, which we think mobilizes the normal antibodies of the circulating fluids to the affected part. There seems to be some evidence that this is associated with the production of blood engorgement, as is evidenced by increased temperature in affected joints during a protein paroxysm. However, we are by no means out of the realm of theory at the present time.

It must be quite evident that there is a difference between the action of the various protein substances used in the treatment of infections. We have found that the intravenous injection of dead typhoid bacilli and colon bacilli produced no effect in a few cases of pyuria which responded to subsequent treatment with horse serum given subcutaneously. There is a difference in the reaction induced by the various foreign proteins. (Case 5 illustrates this point.) There is no question in my mind that the protein of dead typhoid bacilli is the best protein to use for many of the infections. Bacterial proteins, particularly this one, give a marked reaction whether given intravenously or subcutaneously. Milk, in the few cases in which I have used it, may give little or no reaction subcutaneously. Horse serum intravenously, as we have recorded elsewhere,[2] induces reactions analogous to, if not identical with, those of dead typhoid bacilli. Subcutaneously, it also induces a similar reaction. In our experience it may stop or ameloriate an attack of whooping cough, an attack of acute cervical adenitis (glandular fever) and cause a subsidence of the glandular swellings. But for some reason it has appeared to cure a case of pyuria when the bacterial protein has failed to do so (Case 5).

Kempton,[3] Greenthal [4] and myself have shown that horse serum protects a guinea-pig against several fatal doses of diphtheria toxin when administered to the pig subcutaneously. Greenthal and I have, we think, quite definitely shown that this effect of the horse serum is due to a substance aside from the protein that neutralizes, or antagonizes, the action of the toxin. The albumin, or the globulin of horse serum freed from this substance, has no effect in preventing the fatal effect of diphtheria toxin. The globulin must be attached to this anti-substance before it can be effective. We are unable to separate the anti-substance from the globulin. Now, diphtheria antitoxin, when administered in these infections, acts in the same way. Hence we are at a loss to say whether pyelitis or pyuria is benefited by the protein of the horse serum or the combination of protein with antisubstance. Evidently the effect does not depend on hyperemia as a result of hyperallergy, for in other cases we have seen that beneficial effects sometimes come with the first injection, ahead of the development of the symptoms of serum disease. Hyperemia may occur under this condition.

We have several cases in which long controls with other methods aid us in making the statement that horse serum very often clears up a refractory case. I will cite another example.

Ann E. (Case 2), aged 1 year, presented the symptoms of attacks of high fever and gastro-intestinal upsets. Physical examination was

2. Cowie and Calhoun: Arch. Int. Med. **23**:131 (Jan.) 1919.
3. Cowie and Kempton: J. M. Research **42**:227, 1921.
4. Cowie and Greenthal: J. M. Research **42**:261, 1921.

negative, except for the finding of pus in an acid urine and the presence of colon bacilli. The case was treated by the usual methods for several months, but the attacks continued to recur. It was hoped the case would recover without the necessity of sensitizing the child to horse serum. This proved to be unsound reasoning, as a pyelitis might be quite as serious a disease as the ordinary case of diphtheria for which we would not hesitate to give a dose of antitoxin. At my request Dr. Kempton gave a dose of 3 c.c. of horse serum subcutaneously. This ended the condition. In the course of two or three days the pus had disappeared from the urine and has not returned to date (now over 3 years).

On the other hand, and this seems a strange coincidence, an adopted sister of this little patient (Case 3), a girl, aged 3 years, developed the same symptoms about two years later (attacks of high fever) but in a more aggravated form, which have persisted off and on for more than nine months. Many horse serum injections have been given without the slightest effect in clearing up the pus which is visible to the unaided eye, and which has been proved by Dr. Cabot to be coming from the right kidney. This examination showed that the bladder walls were clear, the orifice to the left ureter patent, the orifice to the right pouting, and the passage of the catheter into the ureter obstructed one-eighth inch above the bladder, while the catheter passed readily into the left kidney, from whence clear urine proceeded to flow.

I am reporting these experiments, not with the idea of advocating the general adoption of this method of treating pyogenic infections of the genito-urinary apparatus, but from the standpoint of interest in developing a knowledge of the action of nonspecific foreign protein in disease process. I am definitely opposed to the indiscriminate injection of alien substances into the body. They may eventually prove to be absolutely noninjurious but at the present time we certainly know too little about the ultimate results of the injection of so many substances—pollens, vaccines, vegetable and animal proteins of various kinds, as well as of carbohydrates and salts. The point we wish to clear is whether the unquestioned cure in a few cases is due to the protein, the antisubstance, or the combination of protein and antisubstance.

REPORT OF CASES

CASE 1 (No. 4-3427).—Sarah R., aged 9 years, entered April 9, 1917, complaining of sharp cutting pains in right side and fever. Pus in the urine was treated with hexamethylenamin without relieving the condition. There was definite response to horse serum injections, as noted by distinct clearing up of the urine. Patient left the hospital before the urine was perfectly clear.

Comment.—The only value this case affords is the fact that following the horse serum injections there was definite improvement while previous treatment had brought about no change. It is well known, however, that pyelitis, untreated, may clear up to reappear again after a number of days.

CASE 2 (No. 5-2676).—Walter N., aged 3½ years, entered the hospital, Aug. 15, 1917, for chronic nephritis and dermatitis exfoliativa. This patient also had a marked pyuria, colon infection.

The diagnosis was pyelonephritis.

He had been treated by the alternate alkaline and acid method and hexamethylenamin over a long period. Two injections of horse serum of 3 c.c. each cleared the skin up quite promptly but not permanently. No effect on the pyuria was secured from the horse serum treatment in this case.

CASE 3 (No. 6-4679).—Mary McG., aged 9 months, entered the hospital, March 23, 1919, for failure to gain weight, pyuria, colon bacilli. Acid and alkaline treatment was employed until April 26 when she was given 200 million dead typhoid bacilli intravenously. April 30 another similar dose was given. No improvement followed. May 19, she was given 5 c.c. horse serum subcutaneously. Symptoms of serum sickness developed. Patient was discharged May 24. The pus cleared slowly but a slight temperature elevation persisted. She returned June 1, having gained 12 ounces in weight. She was taking food normally and made no further complaints concerning the pyuria.

CASE 4 (No. 7-4941).—Zona M., aged 5 years, entered the hospital, Oct. 23, 1919, with frequent urination, thirst, following an attack of mumps, pain and tenderness in the back at the site of the right kidney, and fever from 103 to 105 F., during the last four days. She was admitted as an emergency case. A catheterized specimen of urine was acid and contained albumin and pus. Physical examination was negative.

November 17: Patient had been treated by forcing fluids. There was a definite improvement, as recognized by a subsidence of the fever, gain in weight and the development of a good appetite. The pus in the urine was lessened but still quite marked. Four cubic centimeters of horse serum was given subcutaneously. No reaction following this injection.

November 25: Albumin, faint; few pus cells.

December 2: Albumin negative, few pus cells; 2 c.c. of horse serum given subcutaneously.

December 4: Few pus cells; 4 c.c. horse serum given subcutaneously.

December 11: Few pus cells. Patient developed measles.

Jan. 6, 1920: Catheterized specimen of urine shows only an occasional leukocyte. Colon bacilli, positive.

January 7: Two leukocytes in ten fields.

January 8: Only occasional leukocytes.

January 17: No leukocytes found.

Comment.—It will be noted in this case that the greater improvement occurred after the patient had had measles, although prior to that time there was no question as to the reduction in the number of leukocytes.

CASE 5 (No. 8-4863).—Robert C., aged 8 years, entered the hospital Sept. 5, 1919, with remittent fever, marked pyuria and colon infection. Alkaline-acid treatment was not followed by improvement.

November 11: Horse serum, 5 c.c.

November 18: Tonsillectomy.

November 20: Serum reaction from horse serum.

December 2: Reaction subsided; 2.5 c.c. horse serum.

December 4: Five cubic centimeters horse serum. A slight excess of leukocytes in the centrifugated sediment.

After the first horse serum there was improvement in the amount of pus. Tonsils were removed soon after this and pus reappeared in the urine. On discharge there were a few cells found in the sediment. Marked improvement. Discharged Dec. 18, 1919.

CASE 6 (No. 9-5202).—Gale W., aged 9 years, entered the hospital, April 9, 1920, with pain in right hip joint, delirium, fever, 103 F., nosebleed, pus in urine. Sudden onset four months ago (January 15). Pain began in right hip over trochanter major requiring morphin; pain on motion of the right leg. This continued more or less for a week when fever developed, with delirium and nosebleed.

Cystoscopic examination showed pus from both ureters. Urine from right kidney showed colon bacillus; urine from the left kidney *Staphylococcus albus.*

Alkaline-acid treatment, hexamethylenamin, then back to acid-alkaline treatment. No improvement was secured. The urine sediment showed *Staphylococcus albus.*

May 25: Leukocytes, 12,000. Pus continues in the urine. Five cubic centimeters horse serum subcutaneously.

May 27: Urine is still cloudy, thick mucus-like sediment containing much pus; settling out after twelve hours in the test tube shows one third by volume. Five cubic centimeters horse serum subcutaneously.

June 6: Marked symptoms of serum sickness.

June 8: Serum reaction continues; temperature 103 F.; pain in joints; marked itching.

June 10: Serum reaction subsided; considerable mucus but no pus cells found in urine, fourteen days after last horse serum.

June 14: Discharged apparently well; urine entirely negative.

June 24: Doctor writes pus again in urine. This was diagnosed macroscopically.

Comment.—In this case there was immediate effect from the horse serum but apparently it was not permanent. We have not been able to get any further urine samples.

CASE 7 (No. 10-6563).—Ellen S., aged 1 year, entered hospital, Jan. 10, 1921. Diagnosis: Pyelonephritis.

Three injections of horse serum. Definite improvement but not permanent. The baby also had marked eczema and cervical adenitis. This condition was apparently cured by the horse serum.

CASE 8 (No. 11-5529).—Evangeline P., aged 7 years, entered hospital, Oct. 1, 1920, with chills, fever up to 105 F., diarrhea of six weeks' duration; no pain. Physical examination negative, except pulse, 120; temperature, 102 F.; systolic murmur at the apex and aortic area; no thrills; all of which disappeared after a few days in the hospital, no cardiac enlargement.

Urine: Acid; albumin, positive; pus, marked.

October 4: Fever, 102 F. Catheterized specimen for culture contained pus. Hexamethylenamin, 10 grains, four times daily.

October 9: No improvement. Culture shows colon infection. Hexamethylenamin stopped. Salol treatment begun.

October 12: Pus continues; no change.

October 13: Pus continues; no change. Salol stopped; 5 c.c. horse serum subcutaneously.

October 14: Pus the same.

October 15: Pus the same.

October 18: Pus the same.

October 20: Pus the same.

October 29: Pus the same.

November 2: Pus the same.

There has been no reaction from the horse serum (5 c.c. subcutaneously).

November 4: Pus the same, no change.

November 6: Five c.c. horse serum, subcutaneously.

November 10: Pus is very much less in amount.

November 15: There has been practically no pus since November 10. Temperature normal for two weeks.

November 17: Five c.c. horse serum.

November 18: Only a few leukocytes. Catheterized specimen. Culture examined twelve and thirty-six hours, and three days later. No fermentation, no motile bacilli present.

Colon infection has apparently completely cleared up.

CASE 9 (No. 12).—A girl, aged 17, observed by Dr. Kempton, gave a history of eight or ten attacks of chills, high temperature, and abdominal pain over a period of two years. Examination of the urine during the last attack showed abundance of pus and colon bacilli.

Following intramuscular injection of 10 c.c. of horse serum, the temperature fell to normal the following day and remained normal. The urine, however, continued to show considerable amounts of pus until after a very severe attack of serum disease which occurred on the ninth day. Following the attack of urticaria, four examinations of the sediment showed only occasional pus cells. Laboratory records show a temporary decrease in the amount of pus the day following the injection. Eight months have now elapsed with no recurrence of symptoms of pyelitis.

July 19, 1921: Leukocytes, 11,500; pus, four plus; colon bacilli.
July 26: Pus, two plus.
August 12: Pus, three plus.
August 13: Intramuscular injection of 10 c.c. horse serum.
August 14: Improvement; normal temperature; pus, minus.
August 15: Pus, two plus.
August 16: Pus, two plus.
August 19: Macroscopic pus; not examined.
August 22: Serum disease.
August 24: Only occasional leukocyte.
August 25: Only occasional leukocyte.
September 8: Only occasional leukocyte.
September 15: Only occasional leukocyte.[5]

5. Personal communication.

DYSKERATOSIS DIFFUSA CONGENITA*

CORNELIA DE LANGE, M.D., AND J. C. SCHIPPERS, M.D.
AMSTERDAM

REPORT OF CASE

History.—The infant was born normally at term. It cried directly after birth and the meconium and urine were evacuated before the child had anything by mouth. It is the first child of healthy parents. There is no history of miscarriages or of tuberculosis.

Examination.—When 1 day old the baby was examined and it was noted that the skin had a yellow brown color and resembled parchment. The epidermis was for the greater part detached from the underlying layers. There was no sign of trauma except in the groins, which showed some excoriation, and where the underlying stratum was traumatized, the corium was laid bare.

There was much secretion from the vagina. The face was quite devoid of expression and resembled a plaster cast. The eyelids of both eyes showed signs of ectropion. The conjunctiva was of a bright red color. The mouth was very large and always open like the mouth of a fish. The somewhat ectropied lips showed radial fissures. Nothing special was noted inside the mouth.

As far as could be ascertained, the chest and abdomen were negative. Neither the palms of the hands nor the soles of the feet showed any sign of pemphigus. The hair was normal, the ears were well shaped, although their outlines seemed a little vague on account of the peculiarities of the skin.

The patient was brought to the hospital on the evening of the same day, when the following was noted. The child drank and cried normally. The skin was torn here and there and was beginning to come off in big patches. The underlayer of epidermis was somewhat reddened, but appeared to be normal except for some fissures extending down to the corium. Later on the shedding of the skin increased, extending over the trunk, the head and the extremities.

Aug. 28, 1921: General condition was not unfavorable. The shedding of the skin continued.

August 24: Large patches of skin hung loosely from the trunk, arms and legs. The light red underlayer generally appeared to be normal, except for some fissures here and there.

The patient became restless and showed attacks of tremor of considerable amplitude (especially in the arms), which subsequently extended over the entire body.

Examination of the Blood.—Hemoglobin (Sahli), 123 per cent.; red cells, 8,360,000; white cells, 11,000; polymorphonuclear neutrophils, 30 per cent.; eosinophils, 0.3 per cent.; basophils, 1 per cent.; lymphocytes, 48.3 per cent.; transitionals, 8 per cent.; myelocytes, 11.8 per cent.; Türk's forms, 0.6 per cent. When making the differential count of 350 white cells, ninety-three normoblasts and two megaloblasts were seen. The chromocytes were well shaped. There were some megalocytes. Metachromasia was apparent. Large lymphocytes were strikingly few in number; the majority of the lymphocytes being of the smaller type with little protoplasma, the blood platelets were for the greater part of a large size.

Course.—Death occurred in the evening.

EXAMINATION OF SKIN

A complete postmortem examination was not permitted, so we could only examine the skin of the back and of the chest. The stratum

* Received for publication, May 20, 1922.

* From the Hospital for Sick Children.

corneum in some places was of normal thickness, whereas in other places it was either thicker or thinner. The border of the horny layer was irregular. The stratum corneum and the stratum granulosum could be differentiated. It is remarkable that all over the stratum corneum, even in its most peripheral parts, here and there nuclei were found, some of which stained easily with hematoxylin, whereas others did not stain at all. Normally, this layer has no nuclei. In other preparations the stratum corneum has a perfectly normal appearance and, again, in still others it looks like a coagulated mass—the product of combustion without the charred surface.

The stratum granulosum is nowhere well developed and the quantity of keratohyaline substance is doubtless less than in normal cases

The structure of the rete Malpighii is irregular. The papillae are of various sizes, some of them being very large. The papillae do not run parallel to each other, but in different directions. The epithelium

Fig. 1.—Large patches of skin are seen to hang loosely from the chest and shoulders.

is irregular and unequal. There is no edema worth mentioning. The thickness of the epidermis varies considerably in different places. There are no symptoms of inflammation, although the blood vessels are very full, which, however, is a physiologic characteristic of this age. Neither the sweat glands nor the sebaceous glands show any abnormality. Thus, in this case, it is not a question of hyperkeratosis but of dyskeratosis diffusa congenita. The abnormal stratum corneum cannot prevent the skin from drying in.

An examination of Figures 1 and 2 leaves no room for doubt that the case is one of ichthyosis congenita, or, strictly speaking, keratoma diffusum universale congenitum (Kyber), the term ichthyosis being erroneously, and too often, applied to this disease. Indeed, the descriptions of cases published by different authors present such a striking resemblance that, as one of these authors humorously remarked, every one of them might have committed plagiarism of the same case, without being detected.

The first description (by Richter) of this rather rarely appearing cutaneous disease dates back to 1792, and since then the subject has never ceased to interest medical authors. In 1921 two extensive articles appeared, one by Golay [1] and one by Hess and Schultz,[2] besides a short report by McAustin.[3] In 1849, this disease was discovered by G. Vrolk.[4] Both he and Müller were the first to make histologic preparations. The extensive literature on the subject can be found in the articles of Ballantyne,[5] Riecke,[6] Fulci,[7] Golay,[1] Hess and Schultz.[2] As there is no reason for repeating their reports, we will only point out

Fig. 2.—The face resembles a plaster cast. The mouth is fixed in fishlike position.

the histologic difference between our case and the majority of other cases that have hitherto been described.

Most of these cases are very serious ones and are classified by Riecke as ichthyosis congenita katexochen. The majority of these infants are prematurely born, if they are not stillborn. The retraction

1. Golay: Ann. de dermat. et de syph. **2**: No. 3, 1921.
2. Hess and Schultz: Am. J. Dis. Child. **21**:357 (April) 1921.
3. McAustin: Brit. M. J. **1**:155 (Jan. 29) 1921.
4. Vrolyk, G.: Concerning a Singular Defect of the Skin Observed in a First Infant, Amsterdam, 1849.
5. Ballantyne: Manual of Antenatal Pathology and Hygiene, The Fetus, 1902.
6. Riecke: Arch. f. dermat. u. Syph. **54**:289, 1900.
7. Fulci: Arch. de méd. exper. et d'anat. path. **22**:1.

of the skin causes deformity of the hands and feet. As to the ears and nose, often only the apertures of these structures are to be seen. The skin is fissured all over from birth. In a second group, called by Riecke ichthyosis congenita larvata, various symptoms are less or only partly apparent. Instead of "larvata" we would rather use the term "mitior." In Riecke's third group (ichthyosis congenita tarda) scarcely any symptoms or none at all are to be detected at birth. Still they do appear sooner or later, after days or weeks or months, ultimately presenting the aspect of the second group. After vegetating a little while, these patients generally die of some intercurrent illness.

In many respects our case seems to correspond to Ballantyne's description of ichthyosis congenitor mitior.[8] According to him this group is formed by infants whose skin at birth has no fissures and looks like parchment or collodium (it has been rightly compared by Hess and Schultz to the peal of a puffed apple). Fissures appear later. The limbs of our patient were not deformed. Moreover, the infant was fullgrown and it did not die before the fourth day.

In all cases which have been described previously, the thickness of the stratum corneum on microscopic examination was found to exceed ± 200 times that of normal skin. The extremely strong hornification of the hair-funnels seems to be another characteristic. Moreover, the lack of a stratum granulosum is mentioned by various authors. Fulci was not able to confirm this statement, the stratum lucidum being indistinct. Meyenburg,[9] on finding keratohyalin instead of eleidin in the stratum lucidum, concludes that there must be an extremely rapid transformation from the stratum malpighii to the stratum corneum. Carbone proved the rete malpighii to be hypertrophic. In the case described by Hess and Schultz both the stratum lucidum and the stratum granulare were missing. They explain the condition of the skin by the following theory: Primarily the skin must have been hypertrophic and provided with large papillae, which produced a great number of cells, thus forming a thick stratum corneum. The hypertrophic state is followed by atrophy, except in the horny layer. The papillae grow shorter and flatter and their interstices larger. Hairs, sweat glands and sebaceous glands disappear, whereas the elastic tissue diminishes. Secondary to these atrophic symptoms, the epidermis is fissured and the limbs are deformed as a result of the retraction of the skin. Contrary to this theory many authors reported that the glandular system and hairs were normal. According to Golay, hyperkeratosis is in the class of the "desquamation lamelleuse des nouveau-nés" and Brock's érythrodermie ichthyosiforme. He inclines to Bowen's theory

8. The term keratosis or keratoma should be substituted for ichthyosis congenita.

9. Meyenburg: Diss., Berlin, 1912.

of the subsistence of the epitrichium. Unna [10] clearly explains why it is not allowed in this respect to speak of ichthyosis. In cases of hyperkeratosis, contrary to ichthyosis, the stratum corneum is not only thickened, but also abnormally unelastic and, therefore, insufficient to cover the whole body. This causes retraction and ectropion, which symptoms are not known to occur even in the severest cases of ichthyosis. Ichthyosis generally appears on the extensor surface, rarely on the flexor surface, the face or the neck, and never on the palmar and plantar surfaces. In hyperkeratosis these peculiarities are absent, the disease is a diffuse one. Moreover, keratosis is a congenital disease and ichthyosis is not; the former is familial and the latter hereditary.

With our case of dyskeratosis we stand isolated from the majority of authors who describe the thick horny layer. However, the figure, borrowed by Ballantyne from an article by Caspary,[11] shows a general thickening of all the layers of the epidermis without the stratum corneum being conspicuous in this respect. Caspary's patient was an infant, aged 18 months.

The etiology of this singular disease is unknown. Syphilis seems to be out of the question, but the fact that the parents were related to each other may be an etiologic factor. The disease has been likened to anomalies of the organs of internal secretion, but the results obtained by microscopic examinations of the thymus, the thyroid and the suprarenals are not convincing. The information given by Golay is by far the most interesting. The first, second, fifth and seventh child of a certain woman showed symptoms of keratosis, whereas the other children were normal. During her pregnancy this woman had a great longing for salt. When she was able to resist this desire, her babies were normal. When, on the contrary, she indulged freely in the use of salt, the infants were born with the peculiar skin described above. This was confirmed by her husband. We are not informed of the quantity of salt she took. Golay does not feel inclined to reject, a priori, this etiology, salt being absorbed by the aminotic fluid, which he asserts, alters the normal osmotic relation. Moreover, salt has an unfavorable influence on the kidneys of the mother.

Finally, we want to speak of the peculiarities of the blood in our case. Most new-born children are known to have an increased number of red blood cells and a high hemoglobin percentage, whereas their blood contains some myelocytes and some normoblasts, but in our case these findings were far more pronounced. Golay is the only author who, in describing this disease, gave an account of the condition of the blood. Except for many large mononuclears, he did not find any abnormalities. In some cases of hyperkeratosis, as in severe burns,

10. Unna: Die Histopathologie der Hautkrankheiten.
11. Caspary: Vierteljahrschr. f. Dermat. **13**:3, 1886, quoted by Ballantyne.

a congestion of the internal organs has been reported. Therefore, we searched the case histories of extensive burns, hoping to find there, in the condition of the blood, some analogy with our own case. That our researches were fruitless may easily be understood. In attending a case of extensive skin burn, the physician will, of course, concentrate his attention on the wound and abstain from unnecessary and painful examinations. Thus we are unable to give an explanation of the singular condition of the blood of our patient.

THE THYMIC SHADOW IN INFANTS*

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Reports on this subject have been made in recent medical literature, but the number of systematic investigations have been few, therefore it was thought that a study of the thymic shadow in infants, made at definite periods of their lives, and over a prescribed time, would offer material worthy of report.

For this purpose, a total of 119 new-born infants were examined roentgenologically. The first roentgenogram was made within forty-eight hours after birth; the second, ten days later, and then monthly thereafter, up to the end of the first year of life. Owing to the difficulties which are perfectly apparent, it was not possible to follow up many of these infants after the first month in the manner planned. For various reasons, many failed to return for subsequent examinations and were lost track of entirely. The material at our disposal, however, seems of sufficient interest to warrant this report.

In making the roentgenograms, the following technic was observed: The target-plate distance was 19 inches; spark-gap, 3 inches; milleamperage, 50, and the time of exposure, $\frac{1}{10}$ of a second. Films and double screens were used. Since it is well known (Gerstenberger) that the size of the so-called thymic shadow varies with the respiratory phase, it was attempted to make exposures at the end of full inspiration. Inasmuch as there is considerable discussion in the literature as to what constitutes a thymic shadow, and as to which mediastinal shadows may be due to normal structures alone, it seemed advisable to have some means of checking interpretations. The object of this was to determine two things. First, whether an upper mediastinal shadow, of the type usually interpreted as thymus gland, was obtained in the absence of a thymus, and second, whether the roentgen ray always demonstrates the presence of a thymus gland.

In pursuance of this, a total of fifty-five children were examined with the roentgen ray before postmortem, and the results compared with the actual findings at necropsy. The ages of the subjects ranged from 2 days to 10 years. In some older children, differentiation could be made only with difficulty of that part of the shadow due to the thymus,

* Received for publication, May 8, 1922.

* From the Pediatrics Division of the New York Nursery and Child's Hospital and Department of Pediatrics of Cornell University Medical College.

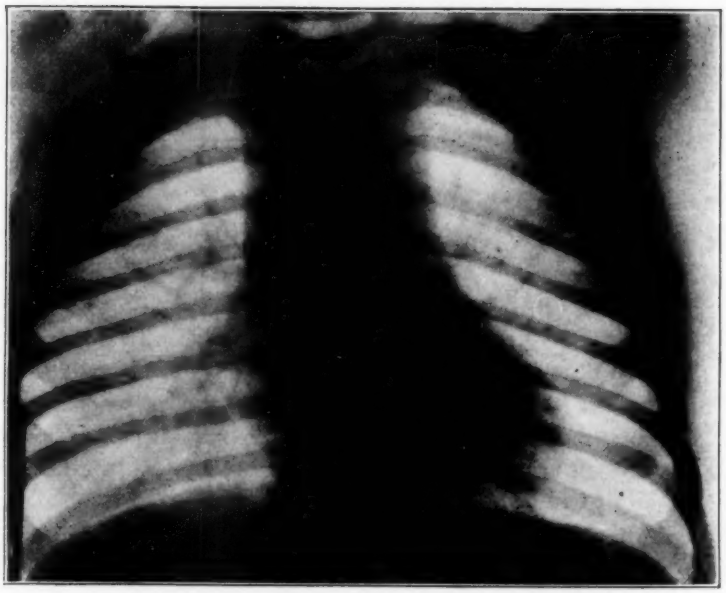

Fig. 1.—Columnar type thymus.

Fig. 2.—Bulbous type thymus.

from that due to other structures, such as glands and blood vessels; and at times this differentiation was impossible.

In thirty-six of the fifty-five postmortem cases, both actual and plate measurements were made for comparison. In twenty-one of the thirty-six cases, the difference lay between 0.5 cm. either way. In seven cases the difference lay between 0.5 and 1 cm., and in eight of the thirty-six it was more than 1 cm. For nonteleoroentgenograms, this was no great discrepancy. In two instances of the original fifty-five cases, there was no suggestion of thymic shadow, yet at the necropsy this condition was found, but in both these cases, the thymus overlay the heart, and was pedicle in type.

The thymic shadows found may be classified into three general types: (1) Columnar; (2) bulbous, and (3) pedicle, all of which are illustrated in the roentgenograms. The pedicled type is eliminated from work on the living, for it is one of difficult differentiation from heart shadow, into which it merges, and can, therefore, be discovered only at necropsy.

For work with the original 119 infants, the findings were divided into three classes:

CLASS 1. *Absent Thymic Shadow.*—This means no shadow apparent in the upper mediastinum, beyond the vertebral transverse processes.

CLASS 2. *A Small Thymic Shadow.*—This was found beyond the vertebral transverse processes, and measured less than 3 cm.

CLASS 3. *A Large Thymic Shadow.*—This shadow measured more than 3 cm. transversely.

This classification was applied at birth, and used throughout investigation. These are absolute terms, used as a working basis. A small thymus may yet be a large one in a chest with small transverse measurements, and conversely, a large thymic shadow may seem small in a large chest. This distinction is important when the question of treatment arises because of size alone.

RESULTS OF EXAMINATIONS

First examination (within forty-eight hours after birth):

Class 1—Absent thymic shadow, 35 cases
Class 2—Small thymic shadow, 34 cases
Class 3—Large thymic shadow, 50 cases

Therefore, at birth, approximately 42 per cent. of the children examined showed thymic shadows measuring more than 3 cm.; that is, shadows which we would read as thymus enlargement and regard as pathologic.

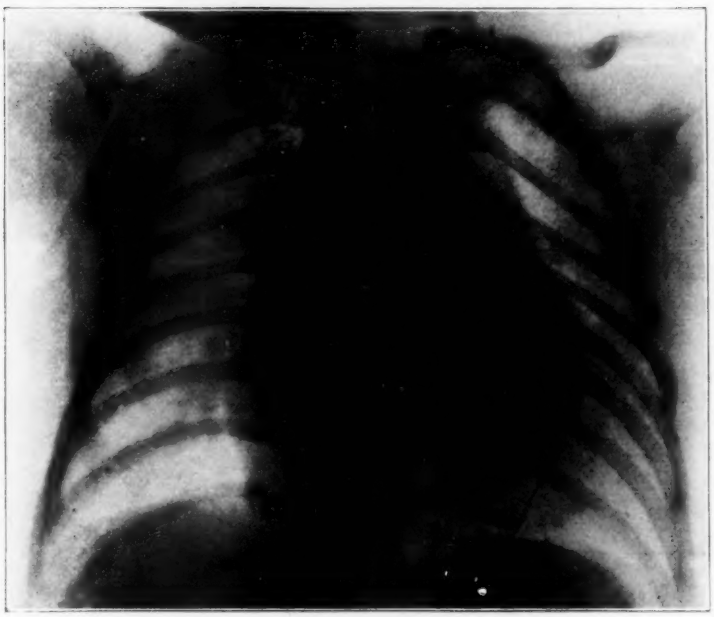

Fig. 3.—Pedicle type thymus.

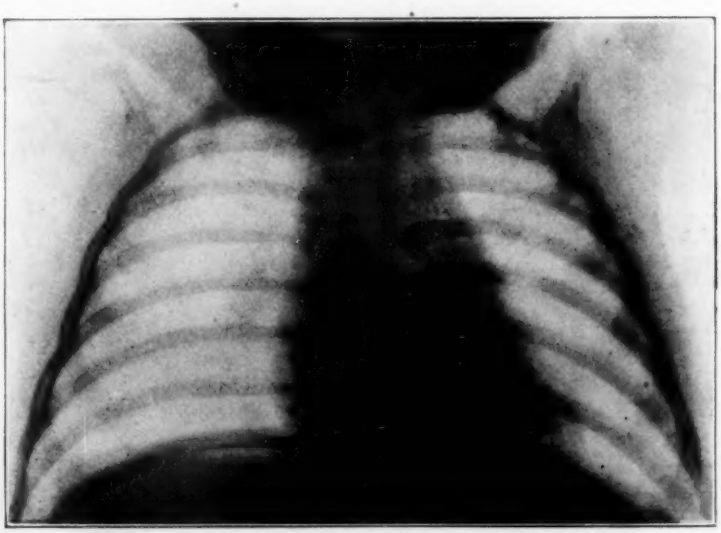

Fig. 4.—Class 1. Absent thymic shadow.

At the end of the first month of life, seventy-three of the original group of 119 children reported for reexamination. Of these, thirty-three were in Class 1; twenty-four in Class 2. Three of these Class 2 glands had definitely decreased in size. Sixteen were in Class 3. One of these glands had decreased in size.

Of a total of forty cases showing thymic shadow, small and large, four had undergone retrogression to smaller dimensions within the period of one month. This was a spontaneous change, for the single roentgen-ray exposure could be eliminated as a causative factor. Of forty-six children, the findings were:

End of Second Month of Life:
- Class 1—15 cases
- Class 2— 6 cases (one had grown smaller)
- Class 3—25 cases (no decrease in size)

Third Month of Life, 39 Children:
- Class 1—13 cases
- Class 2— 4 cases (no decrease in size)
- Class 3—22 cases (no decrease in size)

Fourth Month of Life, 38 Children:
- Class 1—13 cases
- Class 2— 4 cases (no decrease in size)
- Class 3—21 cases (two had decreased in size)

Fifth Month of Life, 31 Children:
- Class 1— 8 cases
- Class 2— 4 cases (no decrease in size)
- Class 3—19 cases (no decrease in size)

Sixth Month of Life, 30 Children:
- Class 1— 8 cases
- Class 2— 4 cases (in one the thymus was confused by glands)
- Class 3—18 cases (no decrease in size)

Seventh Month of Life, 28 Children:
- Class 1— 8 cases
- Class 2— 2 cases (no decrease in size)
- Class 3—18 cases (no decrease in size)

Eighth Month of Life, 25 Children:
- Class 1— 7 cases
- Class 2— 2 cases (no decrease in size)
- Class 3—16 cases (one had decreased in size)

Ninth Month of Life, 22 Children:
- Class 1— 6 cases
- Class 2— 2 cases
- Class 3—14 cases (no decrease in size)

Tenth Month of Life, 17 Children:
- Class 1— 5 cases
- Class 2— 2 cases (no decrease in size)
- Class 3—10 cases (one had decreased in size)

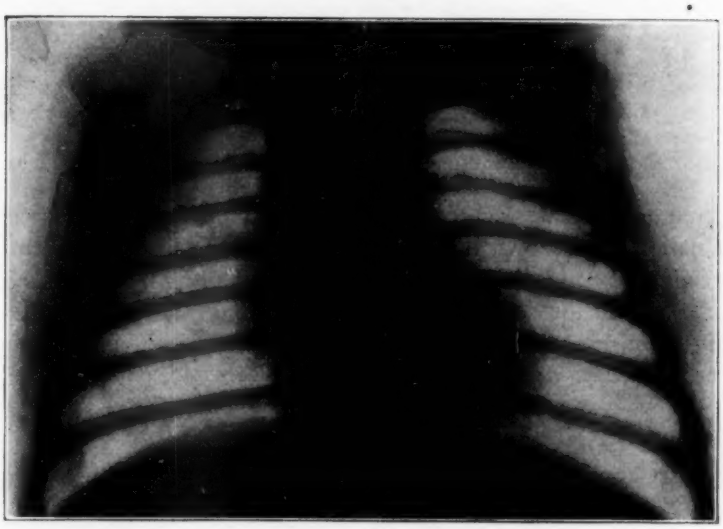

Fig. 5.—Class 2. Small thymic shadow.

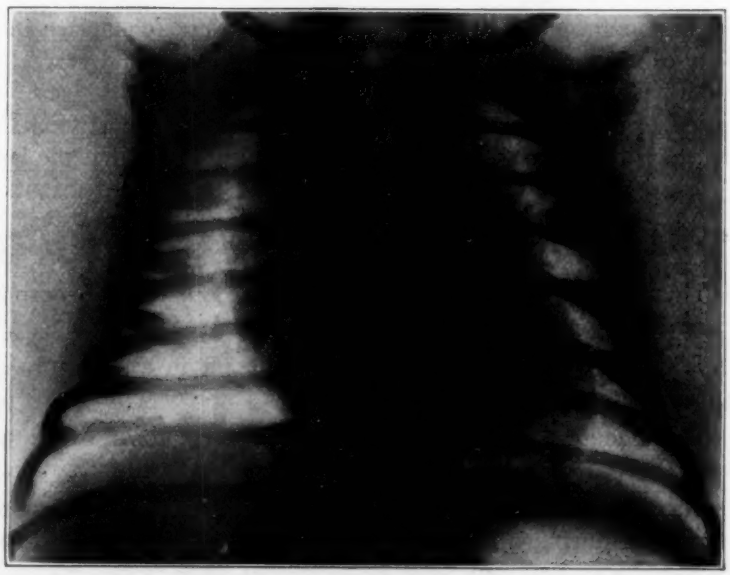

Fig. 6.—Class 3. Large thymic shadow.

ELEVENTH MONTH OF LIFE, 11 CHILDREN:
Class 1—4 cases
Class 2—2 cases (one had decreased in size)
Class 3—5 cases (one was confused with gland shadow)
TWELFTH MONTH OF LIFE, 6 CHILDREN:
Class 1—1 case
Class 2—1 case
Class 3—4 cases (one had decreased in size, and one assumed the shape of the pedicled type)

Some of the Class 1 cases were not reexamined after two successive examinations had shown no change. There were two known deaths in the original group of 119. The first was that of an infant assigned to Class 1, and the second of an infant in Class 3. At necropsy the findings confirmed the classification in both instances. The thymus of the second infant weighed 13 gm.

DISCUSSION

The striking revelation in this study was the fact that in a group of average "normal" infants at birth, 42 per cent. showed the presence of a shadow suggesting a thymus measuring more than 3 cm., and this without gross symptoms. As the work progressed, retrogression in size of the shadow took place, the greatest change within the first few months, a steady change as the year went by, so that with our limited material spontaneous disappearance of this shadow took place in the majority of cases. Some, however, persisted to the second year.

As a rule, the children with large thymic shadows were well nourished, some were large chested, with thick and short neck, and without physical stigmata. The general impression was, that the larger thymic shadows were present in the thick and short necked infants.

CONCLUSIONS

1. Thymic shadows can easily be determined in the new-born and in infancy.

2. Transversely, enlarged shadows are present in a strikingly high percentage of new-borns.

3. This shadow may be present without symptoms or physical stigmata.

4. There is a definite tendency for a spontaneous retrogression of this structure during the first year, but some glands persist beyond this period.

5. There is a type of thymic shadow cast by a pedicle-shaped organ, the mass of which lies on the heart, from which it cannot be differentiated.

6. In the later months of infancy, the presence of large paratracheal glands and prominent blood vessels presents some difficulty in differential diagnosis, but differentiation is possible.

I wish to acknowledge my indebtedness to the Obstetrics and Social Service Departments of the New York Nursery and Child's Hospital for their kind cooperation.

THE INORGANIC PHOSPHATE CONTENT OF BREAST MILK OF MOTHERS WITH NORMAL AND WITH RACHITIC INFANTS *

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The rôle of the phosphorus ion in the metabolism of rickets has recently acquired a prominence which is certain to be of the greatest moment. Clinically, we have learned form the work of Howland and Kramer [1] that infantile rickets, when active, is invariably accompanied by a reduction in the serum inorganic phosphorus and, as shown by Hess and Gutman,[2] this constituent of the blood rises as the rickets heals. Experimentally, the almost simultaneous and quite independent observations of Sherman and Pappenheimer [3] and of McCollum and his associates [4] have shown that rickets can be produced at will in the rat by a diet deficient in inorganic phosphorus, and that if this salt be added to the dietary in sufficient quantity, rickets fails to develop. However striking and conclusive these experimental observations may be, it is at once apparent that in the light of clinical experience they cannot indicate that infantile rickets is merely dependent on a deficient phosphorus supply. We know that cow's milk contains approximately five times as much phosphorus as woman's milk and yet we see rickets far more frequently among bottle fed babies. The question of the factors influencing the availability of an adequate supply we cannot discuss in the present state of our knowledge.

It was in view of the aforementioned studies in rat rickets that an investigation of the inorganic phosphate of breast milk was undertaken. For this purpose samples of milk were obtained from mothers attending the Newly Born Outpatient Service of the Touro Infirmary and their infants, all of whom were exclusively breast fed, were examined for rickets clinically and in some instances by serum phosphorus determinations.

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* Received for publication, May 15, 1922.

1. Howland, J., and Kramer, B.: Calcium and Phosphorus in the Serum in Relation to Rickets, Am. J. Dis. Child. **22**:105 (Aug.) 1921.

2. Hess, A. W., and Gutman, M. B.: The Cure of Rickets by Sunlight Accompanied by an Increase in the Inorganic Phosphate of the Blood, J. A. M. A. **78**:29 (Jan. 7) 1922.

3. Sherman, H. C., and Pappenheimer, A. M.: Experimental Rickets in Rats. I. A Diet Producing Rickets in White Rats, and Its Prevention by the Addition of an Inorganic Salt, J. Exper. M. **34**:189 (Aug.) 1921.

4. McCollum, E. V.; Simmonds, N.; Shipley, P. G., and Park, E. A.: The Production of Rickets by Diets Low in Phosphorus and Fat Soluble A, J. Biol. Chem. **47**:507 (Aug.) 1921.

Methods.—The samples of milk were collected as follows: The infant was allowed to nurse one breast for from fifteen to twenty minutes, after which approximately ½ ounce of the strippings was milked by manual expression. An equal quantity was then obtained of the foremilk from the other breast and the two were mixed. Thus,

TABLE 1.—INORGANIC PHOSPHATE CONTENT OF MOTHER'S MILK AND BLOOD SERUM OF NONRACHITIC INFANTS

Date	Age	Milk Phosphate Mg. per 100 C.c.	Serum Phosphate Mg. per 100 C.c.
11/28/21	2 weeks	4.2	...
12/ 6/21	2 weeks	4.1	...
12/ 8/21	2 weeks	3.9	...
12/ 9/21	3 days	4.8	...
12/10/21	3 months	3.2	...
12/13/21	2 months	6.2	...
12/17/21	5 months	3.0	...
12/21/21	4 months	5.0	...
12/28/21	3 weeks	2.5	...
1/20/22	4 weeks	*	5.8
1/23/22	6 weeks	2.6	...
1/26/22	5 months	4.4	4.6
1/28/22	6 weeks	*	4.1
2/ 9/22	2 months	5.4	5.7
2/11/22	2 months	5.1	5.4
2/16/22	4 months	2.6	4.9
2/25/22	8 months	5.0	4.6
3/ 4/22	3 months	3.3	5.0
Average		4.08	5.0

* Resisted coagulation.

TABLE 2.—INORGANIC PHOSPHATE CONTENT OF MOTHER'S MILK AND BLOOD SERUM OF RACHITIC INFANTS

Date	Months	Rickets Clinically	Milk Phosphate, Mg. per 100 C.c.	Serum Phosphate, Mg. per 100 C.c.
12/ 3/21	11	+	4.3	...
12/15/21	11	+	4.6	...
12/ 8/21	6	+	3.7	...
1/ 3/22	2	+	4.0	...
1/19/22	4	++	5.4	2.2
1/24/22	5	++	5.4	3.0
1/24/22	4	++	4.5	2.7
2/ 2/22	4½	+	5.7	3.6
2/ 2/22	4	++	5.4	3.4
2/14/22	19	++	*	2.5
3/18/22	8	+++	5.1	2.2
2/16/22†	4	±	2.7	4.1
Average			4.8	2.8

* Resisted coagulation. † Excluded from average.

milk from both breasts was obtained, having a fat content probably equal in quantity to that of the entire milk of one breast. The milk was kept in the refrigerator until analyzed, always within three or four hours after milking.

The blood was obtained by longitudinal sinus puncture and the serum used as soon as possible. No plasma determinations were made

for it has recently been shown [5] that a very slight excess of citrate or oxalate added to the blood leads to anomalous results. The inorganic phosphate determinations in the serums and milks were carried out by the method of Bell and Doisy.[6] The concentration of the inorganic phosphates in human milk is such that this method can be used virtually without modification. The only change made in the technic was the addition of 2 parts of the 20 per cent. trichloracetic acid solution to 1 part of milk, instead of equal parts of each. This was done to insure as complete coagulation of the milk proteins as possible. Occasionally a milk was obtained which resisted coagulation and such had to be discarded. A 1:10 dilution was used, both for milk and serum, and the dilute standard which Bell and Diosy recommended for blood plasma (10 c.c. $\equiv$ 0.5 mg. P.) was used for the milk determinations. The results are collected in Tables 1 and 2.

I have excluded from the average the last case in Table 2, in which the evidence of rickets was slight and the serum phosphate was 4.1 mg. My average for the milk phosphate is in excellent agreement with that of Denis,[7] who found in twenty-one samples of mature breast milk an average of 4 mg. inorganic phosphate per 100 c.c., with variations from 2.3 to 5.4 mg. Sixteen years ago Sikes [8] published his results of phosphorus determinations on 300 samples of human milk during the first thirteen days of lactation and obtained somewhat higher figures for his "nonproteid" phosphorus. His average is 7 mg. nonproteid phosphorus in 100 gm. of milk. Holt, Courtney and Fales [9] give as their average for mature milk 7.4 mg. phosphorus per 100 c.c.

SUMMARY

1. Inorganic phosphate determinations of serums of eight nonrachitic infants showed an average of 5 mg. per 100 c.c.

2. Sixteen samples of breast milk of mothers whose infants showed no evidence of rickets contained an average of 4 mg. inorganic phosphate per 100 c.c. milk.

3. The serums of seven rachitic infants were examined and the average value for the inorganic phosphate was 2.8 mg. per 100 c.c.

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5. Denis, W., and von Meysenbug, L.: Note on a Possible Source of Error in the Bell-Doisy Method for Determination of Phosphates in Blood Plasma, J. Biol. Chem. **2**:1 (May) 1922.

6. Bell, R. C., and Doisy, E. A.: Rapid Colorimetric Methods for the Determination of Phosphorus in Urine and Blood, J. Biol. Chem. **44**:55 (Oct.) 1920.

7. Denis, W.: Unpublished work.

8. Sikes, A. W.: On the Phosphorus and Calcium of Human Milk, J. Physiol. **34**:464 (Oct. 29) 1906.

9. Holt, L. E.; Courtney, Angelia M., and Fales, Helen L.: A Chemical Study of Woman's Milk, Especially Its Inorganic Constituents, Am. J. Dis. Child. **10**:229 (Oct.) 1915.

4. The breast milk of mothers of rachitic infants was found to contain an average of 4.8 mg. inorganic phosphate per 100 c.c.—an average which falls within the "normal" range.

CONCLUSIONS

1. There is no reduction in the inorganic phosphate of the breast milk on which infants develop rickets.

2. The finding of other observers that the inorganic phosphate content of the serum is reduced in rickets is corroborated.

INDICATIONS FOR TONSILLECTOMY IN INFANCY AND CHILDHOOD. IS THE MODERN TENDENCY TOWARD UNIVERSAL TONSILLECTOMY JUSTIFIED?*

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During the past few years there has been engendered in the minds of medical men an unbounded spirit of antagonism toward the faucial tonsils. The pendulum has been swinging toward extreme radicalism. The tonsils have been held responsible for almost every disease of childhood. As portals of entry and foci of infection they have been accused of producing every form of pathologic condition. The obsession has spread to the laity who are now, with or without medical advice, demanding the complete removal of the tonsils as a routine hygienic measure.

Last year the medical school inspectors of New York City recommended tonsil treatment for 49,230 children. If the problem were extended to the whole country it would undoubtedly include more than a million children.

Tonsillectomy is quite a major operation. Its risks are very definite. Numerous serious complications have been reported. A large number have not been reported. The indiscriminate removal of the tonsils should be condemned.

I shall outline briefly the history of tonsillectomy, discuss the functions of the tonsils and present an analysis of 200 cases observed in private practice in which the tonsils had been removed for a variety of reasons. I shall endeavor to formulate rational indications for tonsillectomy.

The first account of the tonsil operation was given by Celsus in A. D. 10, who recommended removal of the tonsils if they "remain indurated after inflammation." Aetus, in A. D. 490, writes more conservatively of the excision of the tonsils. In A. D. 1120, Albucasis expressed his fear of hemorrhages after tonsil operations. During the next 500 years the operation was not done. It was revived in 1637 by Servius and criticized later by Dionus, who claimed that the tonsils had definite functions. Meseati and Wiseman were the first to employ it in modern times.

The functions of the tonsils have long been the subject of much study and experimental work, and a large mass of contradictory conclusions may be found in the literature. A careful sifting of the material and critical observation of cases, however, cannot but lead one to the conviction that the tonsils have definite functions to perform.

* Received for publication, May 8, 1922.
* Read before the Thirty-Fourth Annual Meeting of the American Pediatric Society, held at Washington, D. C., May 1-3, 1922.

In our enthusiasm over tonsillectomy, these functions are frequently entirely discarded.

The anatomy of the organs shows that they are practically aggregations of lymph nodes covered by epithelium. Indentations occur forming the crypts.

Like other lymph nodes the tonsils exercise a protective function. They act as a sieve, the "first line of defense" against microbic invasion. Stöhr [1] has shown that the tonsils are traversed by an enormous number of leukocytes which exercise a kind of migration toward the surface.

The work of Adami and Nicholls [2] leads them to say:

> The tonsils appear to have an important function. While the lymphoid cells are themselves, to a limited degree, phagocytic, polymorphonuclear leukocytes in considerable numbers make their way from the blood vessels to the surface through the epithelial covering. These leukocytes are strongly phagocytic and their activity suggests that the tonsils form one of the barriers against the invasion of the system by pathogenic micro-organisms.

Henke [3] proved by numerous experiments that there was a constant lymph current passing from the mucous membrane of the nose and gums through the tonsil to its surface. This must undoubtedly act as a strong force in combating bacterial invasions. The reaction of the tonsil is commonly noted, while the original source of the infection, whether it be in the nose, the accessory sinuses, or in the mucous membrane of the mouth, is entirely disregarded.

The posterior pharyngeal wall, the postnasal space and the intestinal wall contain innumerable lymph follicles similar to those of the tonsil. If this type of structure was especially susceptible as a portal of entry or focus of infection, of what avail would be the removal of the tonsils?

Before antitoxin was introduced, it was common knowledge that diphtheria ran a milder course when localized to the tonsils than when it involved other parts.

Tonsillitis alone, or when associated with other conditions, is usually only a manifestation of systemic infection. If the infection becomes more generalized, it occurs in spite of the tonsil, not because of it.

In rare instances, however, the tonsils may cease to function and become "choked filters" in which cases they may be a source of infection. The diseased condition should be proved before the tonsils are sacrificed.

The rôle played by the tonsils in the production of lymphocytes has been conclusively demonstrated by Wood.[4] He regards this as a most important function. Piersol [5] showed that large numbers of lymphoid cells pass through the tonsils into the oral cavity to become the salivary corpuscles.

1. Quoted by Comroe: J. A. M. A. **63**:1367 (Oct. 17) 1914.
2. Adami and Nicholls: Principles of Pathology **2**: p. 391.
3. Henke: Arch. f. Laryngol. **27**: Pt. 2, 1914.
4. Wood, G. B.: Univ. Penn. Med. Bull. (Oct.) 1904.
5. Quoted by Comroe: J. A. M. A. **63**:1368 (Oct. 17) 1914.

Masini [6] believed that the tonsils developed an internal secretion, similar to the suprarenal gland, but this has not been substantiated by sufficient evidence.

The tonsils have an important part to take in the lubrication of the food as well as of the throat during the act of speaking and singing. I have frequently noted marked changes in the appearance of the tonsillectomized throat. The presence of nodules of cicatricial tissue, of adhesions, and destruction of muscular tissue occur in cases that have been performed not by the tyro in the specialty but by leading rhinolaryngologists. Kenyon and Kradwell [7] have said, "It seems conservative to say that following tonsillectomy the palatoglossus and palatopharyngeus muscles are never wholly normal in their action."

Changes in the speaking and singing voice after removal of the tonsils have been forcibly emphasized by Faulkner,[8] Connor,[9] Kenyon [10] and Freudenthal.[11]

During the last five months I have added to my private case history charts a tonsil record for each patient. The following inquiries were made:

1. Have the child's tonsils been removed?
2. When were they removed?
3. By whom?
4. Why removed?
5. Has the condition improved?

I have selected for analysis 200 consecutive cases in which the tonsils were removed completely by specialists at least six months previous to the time of inquiry.

In 95 per cent. of the cases the adenoids were removed at the operation. The ages of the patients ranged from 15 months to 14 years.

The reasons given for the removal of the tonsils may be grouped as follows:

	Cases
1. Frequent attacks of colds	40
2. Obstructive symptoms (Mouth breathing, difficult nasal breathing)	46
3. Ear and mastoid infections	31
4. Attacks of acute tonsillitis	20
5. Cough	14
6. Enlarged tonsils	10
7. Diseased tonsils	9
8. Malnutrition	9
9. Cardiac and chorea	8
10. Miscellaneous (Speech defect, 2; muscular pains in extremities, 4; asthma, 2; convulsions, 1; no reason given, 4)	13

6. Masini: New York M. J. (Sept. 28) 1898.
7. Kenyon and Kradwell: Ann. Otol., 1916.
8. Faulkner: Med. Rec. **79**:40 (July) 1910.
9. Connor: Texas State J. M. **11**:545, 1916.
10. Kenyon: J. A. M. A. **69**:709 (Sept. 1) 1917.
11. Freudenthal: Tr. Am. Acad. Ophthal. & Oto-Laryngol., 1918.

The symptomatology in the cases in which the complaint was of frequent attacks of colds included chiefly coryza and cough, usually with a slightly elevated temperature. Of the forty cases of this group only fourteen showed an improvement in symptoms after the removal of the tonsils and adenoids. Twenty-six, or 65 per cent., reported no improvement. Definite statements were made in eight cases that the symptoms were aggravated after the operation. I shall discuss some of the complications and sequels later.

The most important symptoms of the obstructive cases had been mouth breathing, clogged nasal passages and snoring at night. Two patients had complained of difficulty in swallowing. Of forty-six cases of this group, reports of cures or improvements after removal of the tonsils and adenoids were given in thirty-five cases, or 76 per cent. In eleven cases no improvement was noted. Of these, eight showed definite evidence of the high arched palate and imperfect coaptation of the teeth. McClanahan,[12] in 1913, called attention to the futility of operation in this type of case.

Of the thirty-one cases of ear and mastoid infections, twenty patients had had tonsils and adenoids removed in order to prevent frequent recurrences of acute otitis media. In only eight of these cases favorable reports were given, i. e., no recurrences or less frequent attacks. In one case a discharging ear developed three days after the removal of the tonsils and adenoids, in another a discharging ear followed by a mastoiditis developed one week after the operation. In the eleven remaining cases of this group the tonsils and adenoids were removed because of persistent ear discharge. In only four cases was the condition said to have been favorably influenced.

Of twenty cases, in which tonsils had been removed on account of frequent attacks of tonsillitis, three patients had developed sore throats at intervals subsequent to the operation. In each of these cases examination revealed a reddened pharynx with prominent lymph follicles.

The tonsils and adenoids had been removed in fourteen cases of persistent cough. In five of these the parents had been told that chronic bronchitis was present, in one case—asthma. Reports of cures were given in four cases. In eight cases the cough was not altered in severity by the operation; in two cases it was aggravated.

In ten cases the tonsils had been removed because of hypertrophy. There had been no symptoms. Subsequent to the operation three patients had developed frequent colds and sore throats.

Reports of diseased tonsils were given in nine cases. There had been no symptoms whatever in four of these. The rhinolaryngologist had

12. McClanahan: Tr. Am. Ped. Soc., 1913, p. 174.

labeled them "diseased." Following the operation, five patients had recurrent sore throats.

Of nine cases of malnutrition, only three had been benefited by the removal of the tonsils and adenoids. In six there had been no more gain in weight than was noted before the operation.

There has been great difference of opinion and of statistics regarding the relation of tonsillitis to articular rheumatism and cardiac disease, from 80 (Faliber) to 1.4 per cent. (Pibram).[13] Recently St. Lawrence [14] presented very favorable results from tonsillectomy in rheumatic and cardiac cases. His patients were under the guidance of a cardiac clinic and received careful medical and social service attention. We cannot but feel that these factors play a considerable part in producing the improvement noted.

Tonsillitis is of very frequent occurrence in infancy and childhood. If the tonsils played an important rôle in the production of rheumatic and cardiac manifestations, should we not expect a greater evidence of these conditions? Is the tonsillitis frequently associated with these conditions not a manifestation of the rheumatic infection?

Of the eight cases in this group only two reported improvement. One cardiac patient had had two attacks of heart failure before the removal of the tonsils. Subsequently, over a period of two years, no attacks of decompensation had occurred. Of the five cases of chorea, three associated with cardiac lesion, four patients had had attacks after the removal of the tonsils and adenoids. Recently, I have seen two cases in which the tonsils had been removed three and five years ago, respectively. Both ran the typical course of an acute rheumatic fever with high temperature and painful, swollen joints. One developed a cardiac lesion.

Of the thirteen cases in which tonsils and adenoids had been removed—for speech defect (2 cases), muscular pains in extremities (4 cases), asthma (2 cases), convulsions (1 case), no improvement had been noted subsequent to the operation.

The statistics I have presented are not submitted as conclusive evidence. The reliability of the statements of parents is not absolute. But the facts are suggestive. Combined with the clinical impressions that I have received for a number of years in hospital and private work they have convinced me that the tonsils have too frequently been sacrificed and the risks of an operation entailed without sufficient reason.

Numerous complications following the removal of the tonsils have been described. In 1912, Koplik [15] called attention to three forms of

13. Quoted from Kyle: Am. J. Dis. Child. **15**:142 (March) 1915.
14. St. Lawrence: J. A. M. A. **75**:1035 (Oct. 16) 1920.
15. Koplik: Am. J. M. Sc. **154**:70 (July) 1912.

infection following the surgical removal of the tonsils: (1) A moderate febrile reaction; (2) an acute or subacute endocarditis; (3) a severe sepsis with profuse hemorrhages and bronchopneumonia.

Dabney [16] described a case of acute rheumatic fever which developed in a child three days after tonsillectomy.

Sewell [17] reported fifty cases of serious hemorrhage with nineteen deaths following the removal of the tonsils.

Cases of general sepsis, pneumonia, lung abscess, subcutaneous emphysema, lung infarct and meningitis following tonsillectomy have been described.

In my group of cases I have seen the development of a definite lung abscess, an acute otitis media followed by a mastoiditis, and three severe cases of pharyngitis after tonsillectomy. During the past three years there were admitted to the pediatric service of Mt. Sinai Hospital seven cases of lung abscess, seven cases of bronchopneumonia and one case of lobar pneumonia which developed after the removal of the tonsils.

In selecting our cases for the removal of tonsils and adenoids we should be guided by safe and conservative principles.

1. If there are obstructive symptoms, mouth breathing (snoring at night) with no evidence of a high arched palate as the cause of obstruction, the adenoids should be removed.

2. If there is a persistent nasal discharge that does not yield to the usual therapeutic measures and in the absence of a sinusitis the adenoidectomy should be performed.

3. If the tonsils are sufficiently large to cause obstruction, difficulty in breathing or swallowing, tonsillectomy is indicated. One must not be mislead, however, by the presence of a large tonsil that appears to be obstructive, a tonsil that is rather pushed out toward the median line by the presence of a deep cervical adenitis. I have described these cases as parapharyngeal adenitis. It occurs most commonly after grippe, scarlet fever and measles.[18]

4. If the frequent occurrence of tonsillitis has produced definite disease in the tonsils, as evidenced by irregularity, raggedness and friability, tonsillectomy is indicated.

5. If there is recurrent accumulation of cheesy material in the crypts of the tonsils, or if on pressure this may be extruded from the tonsils, with the presence of a foul odor of the patient's breath and symptoms of toxic absorption, the tonsils should be removed.

6. In cases of persistent cervical adenitis following tonsillitis, whether by pyogenic or tuberculous origin, tonsillectomy is indicated.

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16. Dabney: Ann. Otol., Rhinol. & Laryngol., December, 1913.
17. Sewell: Med. Chron., July, 1911.
18. Heiman: Am. J. Dis. Child. **10**:104 (Aug.) 1915.

These are the rules I endeavor to follow. But each case must be studied individually, the advantages and risks considered before recommending operation.

In conclusion, may I enlist your cooperation to banish the passionate desire, which is fast gaining ground in the profession, to remove every tonsil, and to substitute more conservative and rational principles.

APPLIED DIETETICS IN OUTPATIENT DEPARTMENTS

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If we recall the conditions prevailing twenty-five years ago in the conduct of outpatient departments in the larger hospitals, we realize much progress has been made. This is most apparent in hospitals connected with medical schools, and is largely the result of the increased use of the outpatient clinics for purposes of medical instruction. When I was a third year medical student I recall distinctly three ward visits in the Children's Hospital as the total of bedside instruction for the year in the course in pediatrics. My memory fails when I try to estimate the extent to which outpatient material was utilized for clinical lectures, but it was very meager. When as a graduate I first took charge of the outpatient department of the Infants' Hospital, clinics were practically as large as they are today. I had one nurse as an assistant, and felt myself fortunate if I could inveigle a fourth year student to help with the histories of new patients. The real burden of the clinic fell on the physician in charge. To work four hours each morning, and to see fifteen patients an hour was the standard of efficiency. Contrast this with a well organized clinic of today, with its corps of graduate physicians and interns, its clinical clerks and social workers, its clinical and roentgen-ray laboratories, the special subclinic for cases of heart disease, tuberculosis, infant feeding, posture, nutrition classes, etc. In comparison, the modern clinic seems to have reached its height of organization; certainly the quality of work is beyond anything conceived as practicable in the earlier period I have pictured. It is reasonable to suppose that the next twenty-five years will bring about other changes and innovations to add to the efficiency of medical care of ambulatory patients.

It is my wish to speak of a comparatively new department, the importance of which is becoming more and more evident as we link the social and economic conditions of the patient with his health problem. I refer to the establishment of food clinics as a very necessary and useful adjunct to the medical outpatient department. So far as I can learn there are very few institutions which have established and operated food clinics of the kind that I have in mind.

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* Read before the American Pediatric Society, Washington, D. C., May 1, 1922.

The Boston Dispensary Food Clinic was started in April, 1918, by Michael M. Davis, then director, and Miss Frances Stern of the Federal Commission of the U. S. Department of Agriculture. Lack of how to select, purchase and prepare food so as to make it appetizing, nutritious, and within the family budget, is common to all classes, but particularly so to those who attend the outpatient clinics of hospitals. The high prices caused by the war accentuated this problem, and were the direct stimulus toward the organization of the clinic. Two rooms in the dispensary were equipped with cooking utensils, stove, furniture and accessories necessary for food demonstration, and the conduct of classes. Beginning with one a week, the clinics in six months were increased to daily morning sessions. When Miss Stern went overseas, the clinic was taken over by Miss Bertha M. Wood, and has since continued under her efficient direction.

The result of three years' experience has recently been reviewed by Miss Stern, in consultation with the food committee of the dispensary. It is with the hope that our conclusions may be of help to institutions planning to establish similar clinics that I venture to bring to your attention the conclusions at which we have arrived.

The purpose of the food clinic may be called a demonstration in applied dietetics. It is intended to assist the physicians of medical clinics in carrying out food treatment. It is distinctly a part of the medical institute, in which the medical, dietetic, social, and economic problems of each case are correlated. It is not a center for the distribution of food, in which respect it differs from the diet or food stations established in many places during the war. It necessarily includes "nutrition classes," but has a much larger scope. The fundamental principle of organization is that every patient accepted must be under direct medical supervision by one who, by virtue of his specialty or experience, may be judged competent to determine the nutritional requirements of the case. A patient, for instance, might be referred by the throat department in the food clinic for a condition of malnutrition, but it would be the duty of the food clinic to see that the patient was given a general medical examination (by the pediatrician or internist) and receive from him directions for dietetic treatment. It then becomes the duty of the food clinic not only to follow the lines of treatment indicated by the physician, but to investigate through social service the home conditions, economic resources of the family, and when necessary, to bring the case into relation with proper agencies of help.

The organization of the food clinic and its relation to other departments should be prescribed very distinctly. There are many possibilities of friction and misundertandings, which we have experienced. Conflicts between social service and food workers may occur. The

special department may not take kindly to the fact that its patient has been referred by the food clinic to a general medical or pediatric department. There are possibilities that the internist or pediatrist may feel at times that the dietitian has "taken the case out of his hands" or overstepped her authority. These are pitfalls into which any food clinic will fall if it is allowed to organize as a separate department without direct medical supervision. This medical supervision should be directly exercised within the food clinic, in order that all departments may work in harmony. It is not reasonable to expect that the dietitian or technical food worker is sufficiently familiar with the medical side of her cases to act at all times wisely without the advice of a physician, and she is more likely to seek that advice if she is responsible to a physician of the food clinic alone, than if she attempts to keep personally in touch with all physicians who refer patients to her.

The relation of the social service to the food clinic also is a matter of great importance. There must be a social clinic executive in the food clinic and under the direction of the chief dietitian. The first investigation of the social and economic conditions of the patient would be made by this worker, and her findings reported to the chief dietitian. By consultation it may then be determined in each case whether the continued social work should be conducted by the food clinic, or transferred as a special problem to the general social service department. Subsequent visits to the house are more likely to be made by the food worker or assistant dietitian.

In general, the organization of the food clinic is the same as that of any medical clinic and should be on the same plane.

Its special internal organization may be outlined as follows: (1) Administrative; (2) dietetic; (3) educational.

1. *Administrative.*—The head of the food clinic should, for reasons already given, be the medical consultant. To him the chief dietitian must be responsible. His duties are primarily medical, referring to the internist or pediatrist cases, which, in his judgment, require extended medical investigation, or taking the responsibility of passing the case directly to the dietitian, on the basis of his own examination. He keeps in touch with the general progress of the cases and sees that the patients report back periodically to the special clinics from which they have been referred. He is responsible for the exclusion of contagion from demonstration classes, and gives medical instruction in applied dietetics to classes, to graduates, and undergraduates.

The other members of the staff are the chief dietitian and her assistants, the trained nutrition worker, the social worker, and the clinic executives. These constitute the real working force of the food clinic, but they carry out the food treatment prescribed by the referring

physician, or in case no specific directions have been made, the food treatment as prescribed by the medical consultant of the clinic. It is clear that a competent dietitian will be allowed to act on her own initiative in many cases, such as obesity, constipation, under-nourishment, but there are other groups such as renal, cardiac, diabetic, and tuberculous, which require close and frequent medical supervision—cases which the dietitian is not capable of handling alone. These must be seen frequently by the physician, who must either take the medical responsibility upon his own shoulders, or see that it is properly placed on the referring department. I cannot too strongly emphasize the importance of such medical supervision being directly exerted within the food clinic. It is quite possible that if the size of the clinic warranted, there might be several medical consultants in charge of special classes, as for instance—diabetic classes and children's nutrition classes, adult nephritic and cardiac classes, problems which would probably appeal to different types of medical food specialists. These patients, it should be distinctly understood, are not "taken out" of the medical or pediatric departments. The medical supervision exercised within the food clinic is designed only to guard against errors which might occur from lack of medical knowledge on the part of the dietitians, and to correlate the work of the medical and food clinics. The patients must, therefore, report back to the referring clinics periodically and may attend the food clinic only so long as they are medically supervised.

A food clinic should have a special record card which shall show the salient points in the medical history and physical examination, the particular object which the food clinic should strive to attain, and the date on which the patient shall report back to the medical clinic for reexamination, consultation, and advice. The liaison between the referring department and dietitian should be the medical supervisor of the food clinic, rather than the dietitian herself.

2. *Dietetic.*—The dietitian has her own definitely defined functions which she exercises directly or through her assistant workers. Briefly, these may be enumerated as follows:

I. To determine the family budget, and its possibility of supplying the necessary food which the diet calls for. It is a waste of time to order diets if there are no funds to purchase them, or no knowledge of how to prepare them. The dietitian may in her experience be able to advise a cooperative mother how to readjust her expenditures, so that the proper food may be provided, and she can instruct her in the art of utilizing cheaper products to attain the same end served by the more expensive foods.

II. When the budget is hopelessly inadequate, it is the duty of the dietitian to secure through existing associations such help as may be needed in the way of food or money, and to see that this aid is properly

applied. Diet kitchens and various associations for meeting distress through contributions of food have found it profitable to appropriate a portion of their funds to the food clinic, to be used for emergency and food treatment, as they are thus saved the overhead and complications incidental to social and medical investigation and continued supervision. It is obvious that it is advantageous to carry a case through one institution, supplying all the requirements, medical, social, dietetic, then to link it up with several separately organized and operated agencies, no one of which does a complete job.

III. Selection and preparation of the food is no less important than the question of finance. We cannot assume the responsibility of dietetic treatment unless we provide instruction as to the simple facts relating to food, the methods of preparing it, etc. This has to be done in two ways: (a) by demonstrations in the class to groups of mothers and children; (b) by home visits in special cases by the food worker to help the mother apply the principles taught in the class.

IV. In our larger cities we have a very cosmopolitan population to deal with, much of it recently arrived. The average clinician knows little or nothing of the food values of Jewish, Italian, Syrian, Armenian, and similar diets. It is the duty of the dietitian to be able to think in the terms of the race she is dealing with. We cannot force an American diet at once upon all these people, but we can see that our dietitian, utilizing the foods of the nationality in the case, applies the principle of the medical foods treatment in foods familiar to them. The trouble is often due to improper balance of food which is in itself good, and we are more likely to gain the cooperation of these recent arrivals if we correct what is bad in their habits and customs, instead of trying to force an entirely new dietetic regimen upon them.

V. Still another function of the food clinician is the conduct of classes which have a special objective. We have, for instance, established classes in (1) obesity, (2) constipation, (3) malnutrition, (4) diabetes. The chief value of the group method of instruction is, of course, to economize time and effort so that the largest possible number may be reached at the minimum cost. If, however, there is no periodical medical supervision of the results of such group instruction, the best results cannot be obtained. The medical supervisor of the food clinic must be keenly interested in the work of the clinic, must feel that however much he depends upon the dietitian, the responsibility of getting results is his. This means close observation of each case, and the early separation from classes of those who are not progressing favorably, so that they may be subjected to special investigation. Practically, the routine of class and group work is carried on by the dietitian and her assistants. The medical supervisor takes as his special problem the cases that are lagging or making no response, and in his larger medical experience endeavors to supplement the efforts of the dietitian.

The nutrition class for undernourished children is one of the more important special groups of the food clinic. Such classes are being extensively organized throughout the country. The movement will undoubtedly accomplish a great deal in awakening interest in matters pertaining to nutrition, and in improving the health and physical development of the children of the country. The problem of handling the undernourished child is not, however, as simple as the layman might infer when he sees untrained persons qualify as chief nutrition workers after a two weeks' course of instruction. Malnutrition, if severe, is always primarily a medical problem, and requires close and continued supervision. The food clinic established in connection with a well organized outpatient department is the logical place for the establishment and operation of nutrition classes, which may serve not alone to meet the needs of patients drawn from the clinics, but as a school for the proper training of nutrition workers. There they can learn by actual observation the extent to which these problems of nutrition are linked with medical, social, and economic conditions, and obtain a better perspective than they are likely to under present conditions.

3. *Educational.*—The food clinic organized along the lines I have indicated would offer training to students in medicine, public health, child welfare, nursing, dietetics, and social service. The clinic executive should be a person qualified to instruct in the principles governing the organization and administration of the clinic, and the part played by social service in furnishing information to the dietitian and to the medical supervisor. The food clinician is thus free to give all her time to food instruction, helping the patient to carry out the physician's food prescriptions by virtue of her more intimate knowledge of the technical problems connected with food and its preparation for the accomplishment of specific purposes. Medical students are for the most part uninstructed in these details, and might profit greatly by didactic lectures and demonstrations given by the dietitian.

The medical consultant may also utilize the facilities of the clinic to instruct those interested in public health problems in the medical aspect of cases requiring food treatment, and in the part which continued and systematic medical supervision of the cases plays in attaining the ends sought for. Students in public health would therefore receive instruction by: (1) visits to medical clinics to observe the relationship of food clinics to other clinics; (2) work in the social service department; (3) case instruction based on actual cases, illustrating the prescribed diets in different diseases and conditions; (4) laboratory technique, as a necessary factor determining food treatment in certain diseases, such as diabetes; (5) methods of recording data; (6) educational methods employed in group teaching, as in the case of

nutrition classes; (*7*) the literature of dietetics—including sources of information and recent works bearing on the subject of applied dietetics.

The food clinician must keep in touch with health work and publications. It should be her duty to select and prepare posters, charts, and exhibits, both for the instruction of the student and as a means of getting food ideas into the minds of her patients.

The subject of health has become a national asset. It is exploited by the newspaper, magazine, and civic organizations. Hygiene and dietetics are becoming the life work of innumerable people, some with an excellent foundation for learning, but many with a mere smattering of knowledge. The medical schools of the country are awakening to the need of authoritative teaching on these subjects of such importance to the welfare of the nation—but to be truly effective, such departments or schools of public health must have their clinics, and these must be established in connection with hospitals and dispensaries, where the principles of applied hygiene and dietetics may be studied in their practical applications.

The food clinic—whether one adopts the name or not is unimportant —should, it seems to me, become an established department of every well-organized clinic for the treatment of ambulatory patients. The plan which I have outlined has in part been effected in the Boston dispensary, and represents the general line along which we are attempting to perfect our organization. Its development will depend upon the extent to which public opinion supports the idea. We pediatricians, who are so largely concerned in the problem of nutrition, and food as a means of attaining it, can by our support of the idea of a food clinic do much to put applied dietetics upon a scientific basis, and greatly influence the public opinion as to its importance. At the same time, by the precept and example of well regulated food clinics, we may do much to clarify the subject of food in relation to diseases in our own minds, in the minds of students and hygienists, and ultimately in the thoughts and lives of the general public.

ACUTE INFECTIONS OF THE URINARY TRACT IN INFANTS AND CHILDREN SUBSIDING WITHOUT THE APPEARANCE OF PUS IN THE URINE*

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Since Escherich, in 1898, demonstrated infections of the urinary tract with the colon bacillus in infants and children to be extremely common, the subject has been discussed from almost every point of view. The route by which the infection gains entrance to the urinary tract is yet to be decided, as recently pointed out by Helmholz.[1]

In looking over the literature for the past twenty years, it is interesting to note that practically nothing new has been added during the past ten years. In 1910, I published an analysis of twenty-five cases,[2] the first dating 1901, which included virtually every clinical phase of the disease.

The one characteristic symptom is the sudden onset with high fever, frequently as high as 105 or 106 F. There is often no other symptom and the child does not seem to be "sick" enough to correspond to the degree of fever present, so that we are often in doubt as to the accuracy of the thermometer. The child may and frequently does continue to play with its toys, especially if there is no marked irritation of the bladder or urethra. In other cases, the symptoms are extremely severe, especially in the spasmophilic child.

It is generally conceded that the diagnosis must be finally decided by critical microscopic examination of the urine. The generally recognized requirements for the examination of the urine are as follows: (1) a catherized specimen in a female; (2) a thorough cleansed meatus in the male; (3) the urine to be examined immediately.

If in an uncentrifuged specimen with a hanging drop, low power, colon bacilli in numbers, and pus cells to exceed ten to the field, are present, a diagnosis of cystitis or pyelocystitis is conceded.

My thesis is: that the appearance of pus cells above a point considered normal is not necessary to establish a diagnosis of an acute infection of the urinary tract.

In 1910,[2] I pointed out that I had frequently found colon bacilli in great numbers in fresh acid urine, accompanied with characteristic symptoms, without the appearance of pus, and again in 1914,[3] I pointed

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* From the Department of Pediatrics, University of Minnesota.

1. Helmholz: Am. J. Dis. Child. **22**:606 (Dec.) 1921.

2. Ramsey: Northwestern Lancet **30**:523 (Dec.) 1910; Pediatrics **23**:15 (Jan.) 1911.

3. Ramsey: St. Paul M. J. **16**:343 (June) 1914.

out that: "in many acute infections of the urinary tract, no pus is ever found, the urine containing only bacilli and some epithelial cells. A chemical examination may show a slight trace of albumin or none with the ordinary albumin test. It will, however, usually give a trace of nucelo-albumin, with the cold acetic acid test."

I have repeatedly noticed that after the acute onset of a colon bacillus infection of the urinary tract, with the characteristic high fever, that the urine although acid and containing myriads of colon bacilli remains free from pus for several days, after which pus cells begin to appear in increasing numbers. In other cases, the characteristic symptoms and fever subside after a brief period and the colon bacilli gradually disappear without the appearance of pus in the urine.

It is a well recognized fact that these acute infections with the colon bacillus frequently accompany or follow directly on the heels of some other infection, and that recurrences from time to time are not infrequent.

Colon bacilli in great numbers are found constantly in the urine over long periods of time in chronic bacterurea, and often without pus being present. In these cases the urine is practically always alkaline.

That colon bacilli are frequently present in small numbers in the urine of healthy children has recently been pointed out by Findley and Browning,[4] and confirmed by Helmholz.[5]

It is a recognized fact that mucus membranes generally are subject to infections of every grade of severity. It is rational to assume that the mucus membrane of the urinary tract is no exception to the rule.

It is also a recognized fact that very slight infections of the urinary tract are followed by severe general reactions.

My contention is that many heretofore obscure fevers in infants and children are produced by infections with the colon bacillus, these infections may be local or perhaps systemic, and that they may be diagnosed by the characteristic general symptoms and by the elimination of an increased number of colon bacilli in the urine.

REPORTS OF CASES

CASE 1.—Thomas C., aged 3 years (patient of J. T. H.), was taken suddenly ill, Nov. 7, 1921, with chill and high fever. When seen by his physician a few hours after, temperature was 104.5 F., skin pale, pulse weak and rapid. General examination did not elicit anything to account for the fever. During the following three or four days, the temperature was at times as high as 104.5 F., and other times reached almost normal. Most of the time even when the temperature was high, the child did not feel especially ill and played with its toys. The physical examination remained negative.

Examination of urine, November 7, 8 and 10, showed clear acid urine, no albumin nor pus cells, but greater numbers of colon bacilli. The culture of

4. Findley and Browning: Glasgow M. J. **97**:28 (Jan.) 1922.
5. Helmholz: Am. J. Dis. Child. **23**:309 (April) 1922.

the urine November 10 gave pure culture colon bacilli. The child was put on large doses of hexamethylenamin and large amounts of water, and the temperature became normal in a few days. All bacteria disappeared from the urine within two weeks. An examination, April 20, 1921, showed a normal urine without colon bacilli or anything abnormal.

CASE 2.—Richard M., male, aged 3 years.

During the week of February 14 to 20, this boy had a spot of pneumonia in the right upper lobe. Temperature and symptoms were characteristic of a lobar pneumococcus pneumonia. He was quite sick until the crisis on the seventh day, after which the temperature remained normal for two days. On the night of February 22, he had a sudden chill and when I saw him the following morning the temperature was 105 F. At that time he did not seem especially ill and one would not have guessed the temperature to be nearly as high. The temperature persisted more or less constant for the following forty-eight hours, and gradually reached normal.

Physical examination revealed nothing new to account for the temperature.

The urine passed in a sterile bottle and examined at once gave acid reaction, no pus, no albumin, many motile bacteria, which proved to be colon bacilli. After three or four days, the bacteria disappeared and there have been no recurrences of the fever or other symptoms; the urine remained clear.

CASE 3.—Roy J., male, aged 17 months, has been rather pale for some weeks, but otherwise apparently well, taking food well. April 21, he had a sudden attack of fever; two hours after the onset the temperature was 106 F. plus per rectum. The day previous he had had a little digestive disturbance and the stools were slightly green, with considerable mucus.

A very careful physical examination showed no cause for the fever. The digestive tract was thoroughly cleared out, but the temperature persisted, varying from 103 to 106 F. for twelve hours, after which it gradually reached normal within forty-eight hours.

The specimen of urine passed directly into a sterile bottle was clear, acid reaction, no pus cells, but myriads of motile bacilli. April 23: many colon bacilli, no pus. April 24: colon bacilli, no pus. April 25: colon bacilli, considerable number of red cells, and epithelial cells, probably from the urethra. April 27: no pus cells or red cells, but many bacteria, temperature normal, and feeling very well. May 10: urine clear, acid, no albumin, no pus, no bacilli. Child remains well.

A CRITICAL STUDY OF SIXTY-ONE CASES OF ASTHMA AND ECZEMA IN INFANCY AND CHILDHOOD CONTROLLED BY CUTANEOUS PROTEIN SENSITIZATION TESTS*

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Although the subject of protein hypersensitiveness is a comparatively recent one, a great deal of literature has been published on its various aspects in the past few years. Many writers, among them Baker [1] and Peshkin and Rost,[2] have studied the frequency of the sensitization of the skin in normal persons. Schloss and Walker have also added to our much clearer understanding of the peculiar condition found only in certain persons. O'Keefe,[3] White,[4] Blackfan [5] and Baker [1] also, have made special studies on children with allergic symptoms. Nevertheless, despite all this literature, the use of the cutaneous test as an aid in diagnosis and treatment by pediatrists is still very limited, largely because of a skepticism as to the value of the results secured by this means.

The present study of sixty-one infants and children with eczema and asthma was made to show, if possible, to what extent the use of these tests is advantageous, what better results may be secured by its help, and what its limitations are. That a very large percentage of the children with these syndromes are sensitive to proteins from various sources is not new information. It is an interesting fact, however, that they most commonly derive their symptoms from more than one factor, which necessitates a thorough study of each case. The possibility of a multiple etiology must always be taken into consideration. Focal infection in this type of child plays a very important rôle. The habits of the patient, the diet, and, not of least importance, the home surroundings must be investigated carefully. In this connection, it is interesting to note that a sensitization to rabbit hair is very frequently found. Rabbit hair is commonly employed in the manufacture of articles of clothing such as furs, hats, and slippers, and also in furniture upholstering and bedding.

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1. Baker: Am. J. Dis. Child. **19**:114 (Feb.) 1920.
2. Peshkin and Rost: Am. J. Dis. Child. **23**:51 (Jan.) 1922.
3. O'Keefe: Boston M. & S. J. **183**:569 (Nov. 11) 1920.
4. White: Boston M. & S. J. **178**:5, 1918.
5. Blackfan: Am. J. M. Sc. **160**:341 (Sept.) 1920.

Description of Material Reported.—The material to be reported on herein consists of thirty-one cases of bronchial asthma in children ranging in age from 1 to 14 years, and thirty cases of eczema in infants and children from 5 weeks to 7 years of age (Table 1).

There were twenty-four boys out of thirty-one asthma cases, and seventeen boys out of the thirty eczema cases, thus making almost exactly twice as many boys as girls in our entire group of sixty-one cases.

The nationality of these children was not limited to any one class, and there are included negro and Jewish as well as Irish, Italian, German, Russian and French children.

TABLE 1.—SHOWING THE AGES WHEN THE CHILDREN WERE FIRST SEEN, THEIR AGES AT THE ONSET OF SYMPTOMS, AND THE DURATION OF SYMPTOMS WHEN FIRST SEEN

	When First Seen		When Symptoms Appeared		Duration of Symptoms When First Seen	
Age Periods	Number with Asthma	Number with Eczema	Number with Asthma	Number with Eczema	Number with Asthma	Number with Eczema
Under 1 month	..	..	..	11	..	7
From 1 to 3 months	..	4	..	4	..	6
3 to 6 months	..	4	..	6	1	5
6 to 12 months	..	10	2	3	3	9
1 to 2 years	1	5	3	1	6	2
2 to 3 years	2	2	3	2	3	0
3 to 4 years	2	1	4	0	5	0
4 to 5 years	1	1	7	0	4	1
5 to 6 years	0	0	4	1	4	
6 to 7 years	3	2	0	1	2	
7 to 8 years	3	1	1	1	1	
8 to 9 years	5	None older	2	..	0	
9 to 10 years	3	..	1	..	1	
10 to 11 years	3	..	4	..	0	
11 to 12 years	1	..	..	..	1	
12 to 13 years	4					
13 to 14 years	2					
14 to 15 years	1					
Total	31 cases	30 cases	31	30	31	30

The method of procedure with each case was the same. A complete history and a thorough physical examination were recorded on charts, which forms, along with a sensitization sheet, were attached to the regular clinic records of each child. These served as a very good summary of the findings in each individual case. The children were followed up for as long a time as possible. The real difficulty was in keeping them under active medical supervision for a long enough time. As they improved the visits were fewer and fewer; and those that did not improve rapidly enough, under the treatments instituted, stopped the treatments altogether, as is often the way with dispensary patients. Table 2 will give an idea of the length of time the cases were under active treatment and under observation afterward.

All but five of the cases of bronchial asthma were observed for over one year, nine of them over a year and a half. Twenty of the eczema cases were observed for over one year, and thirteen over a year and a half.

All types of asthma and eczema are included in this report, from the mild to the very severe. No attempt has been made to classify them as to the severity or character of their symptomatology.

As to a family history of hypersensitiveness, eighteen of the cases of bronchial asthma were positive, eleven were negative and two not obtainable. Only fourteen of the eczema cases had dependable histories, ten being positive and four negative. This gives approximately 65 per cent. with positive family histories, which is fairly close to the figures of Schloss,[6] who found 59 per cent. of eighty children positive.

Thirteen of the children with asthma had, either at the time first seen by me or at an earlier date, an eruption which evidently was eczema. Four of these had both eczema and urticaria. Five others had had urticaria but no eczema.

TABLE 2.—SHOWING LENGTHS OF TIME ALL CASES WERE UNDER TREATMENT AND THE TOTAL OBSERVATION PERIOD AT THE PRESENT TIME

Period of Time	Number of Cases Under Treatment		Number of Cases Under Observation	
	Asthma	Eczema	Asthma	Eczema
Under 1 month	3	6		
1 to 3 months	6	10	None for a shorter time	
3 to 6 months	9	10	1	4
6 to 12 months	7	3	4	6
12 to 18 months	6	0	17	7
18 to 24 months	None longer	0	8	6
Over 2 years	..	1	1	7
Total	31	30	31	30

Six of the asthmatic group gave a history of very apparent food idiosyncrasies as follows: 2 to eggs alone; 1 to eggs, beef, and fish; 1 to oatmeal; 1 to mustard; and 1 to oatmeal, pears, cheese and bananas. Ten of the eczema group showed idiosyncrasies to foods as follows: 7 to egg alone; 1 to fish; 1 to egg and wheat; and 1 to egg and oatmeal.

Fluoroscopic and roentgen-ray studies were made in all but four of the asthma cases, and "normal" chests were found in only six. Three cases proved to have tuberculous lesions, one being parenchymatous, which went on to healing, and the other two in the form of tuberculous peribronchial and tracheal glands. The common findings in the remaining cases were a chronic fibrous bronchitis with a diffuse peribronchial thickening and congestion, and very frequently a hilus fibrosis of considerable extent. Emphysematous changes were found in a considerable number.

6. Schloss: Am. J. Dis. Child. **19**:433 (June) 1920.

Of the eczema cases, fourteen were breast-fed when first seen, and four more had been breast-fed at the time of the first appearance of the eruption. In eight cases the eczema had appeared on weaning and in the four remaining children only appeared at the later period of life, when on a much more varied diet than the others.

The Cutaneous Tests.—The cutaneous test was used exclusively in this work. The conclusions of Schloss, who has probably had the widest experience on the comparative value of the cutaneous versus the intracutaneous method, are agreed with by most investigators of the subject. The method of procedure has been described repeatedly in the literature and does not require repetition here.

In interpreting the readings, positive reactions were graded into four different degrees as follows:

1 +, those with a wheal between 5 and 10 mm. in diameter.
2 +, those with a wheal between 1 and 1.5 cm. in diameter.
3 +, those with a wheal between 1.5 and 2 cm. in diameter.
4 +, those with a wheal larger than 2 cm. in diameter.

A single doubtful reaction (i.e. with a wheal greater than the control but not 5 mm. in diameter) was disregarded unless it was present on several repeated trials, when it was taken into the final consideration of the case.

Summary of the Skin Tests Performed.—The skin test was employed in the entire number (sixty-one) of cases here reported; all other cases seen but not tested were omitted.

Complete routine tests were performed in nearly all the cases of bronchial asthma, but this was neither possible nor necessary in the eczema group because of their much more limited diets at their earlier age. In all, 4,520 tests were performed, including 979 repeated tests.

Asthma Cases: A total of 3,722 tests were done on the thirty-one children, 842 of these being repeated tests. This makes an average of ninety-six different proteins tried in each case, plus twenty-eight repeated. The greatest number tried in any case was 139 different proteins with ninety-nine repeated tests, and the least number was twenty-four different proteins.

Eczema Cases: A total of 798 tests were performed on the thirty children in this group, 137 of the tests being "repeats." Thus an average of twenty-two different proteins were tried per patient with from four to five "repeats." The maximum number in any case (on one of the older children) was 110 different proteins with thirty-nine "repeats," and the minimum was four tests on a very young breast-fed infant whose mother refused permission to do more.

In summarizing my results, the repeated tests were not counted individually, but the result with each protein, after all "repeats" were

done, was recorded on the basis of the most constant and probable finding in conjunction with the clinical record of the case.

Number of Positive and Doubtful Reactions.—There were a total of 307 positive and doubtful reactions in all, making only about one in every eleven or twelve tests performed which were either positive or doubtful. There were only 128 positive reactions, making only one in every twenty-eight or twenty-nine tests, an average of two per patient.

Number of Sensitive and Nonsensitive Cases.—Of the asthmatics, eleven showed absolutely no positive reactions and three others only such slight reactions as to consider them finally nonsensitive. The remaining seventeen gave eighty-two positive reactions, and 170 positive and doubtful together. This makes an average of five positives per patient and ten positive or doubtful. There were four with only one

TABLE 3.—SHOWING THE PER CENT. OF NONSENSITIVE PERSONS IN VARIOUS HYPERSENSITIVE GROUPS *

	Type of Cases Studied	No. of Cases	Percentage Nonsensitive
O'Keefe	Eczema in infants	70	24.5
Schloss	Eczema in infants under 16 months	53	24.5
	Eczema in children over 16 months	24	58
White	Eczema in children	56	20
Blackfan	Eczema in children	27	18.5
Strickler	Eczema in children	46	26
Walker	Bronchial asthma in adults and children	400	52
Sanford	Asthma and hay fever in adults and children	800	62.5
Fox and Fischer	Eczema in adults	60	41
Ramirez	Eczema in adults	78	48
Author	Eczema in infants and children	30	43
	Bronchial asthma in children	31	45

* A comparison of the above figures with those of Baker, or of Peshkin and Rost for normal children, is very striking in that positive or even doubtful reactions are extremely uncommon in the latter.

positive, five with only two positive, and three with only three positive, the remainder all showing more than three, and in one case as many as seventeen positive reactions.

Of the eczema cases, thirteen gave absolutely no positive reactions and four others gave only doubtful reactions, which, however, had to be considered as sensitizations because of the clinical findings in these children. The 114 positive and doubtful reactions were therefore divided among seventeen children, giving an average of seven per case. There were forty-six positives alone, in thirteen children, or three and a half positives per patient.

The percentage of sensitive to nonsensitive cases found in children with allergic symptoms varies in different groups studied by different writers. These figures are given in Table 3.

The Reactions Given by the Different Proteins.—The results of the reactions which the various proteins gave are best shown by the summary in Tables 4 and 5.

TABLE 4.—Summary of the Results of the Skin Tests—Eczema Cases

Proteins	Cases	Neg.	4+	3+	2+	1+	±
Asparagus	5	4	..	..	..	..	1
Banana	9	8	..	1	..	..	..
Barley	24	18	..	..	..	1	5
Bean	7	6	..	..	1	..	..
Beef	8	7	..	..	..	..	1
Blackberry	3	2	..	..	..	..	1
Buckwheat	7	6	..	..	..	..	1
Casein	6	5	..	..	..	..	1
Celery	6	4	..	..	..	..	2
Cheese	4	3	..	..	..	..	1
Chicken	15	11	..	..	..	1	3
Coffee	8	7	..	..	..	..	1
Corn	7	5	..	..	1	..	1
Ovomucoid	6	2	1	1	1	..	1
Egg, whole	28	16	..	1	4	4	3
Egg, white	13	5	..	..	3	2	3
Egg, yolk	15	10	..	..	1	2	2
Herring	3	2	..	..	..	..	1
Lactalbumin	7	5	..	..	2	..	..
Lamb	12	11	..	..	..	1	..
Lima bean	6	5	..	..	1	..	..
Cow's milk	29	25	..	..	1	3	..
Mustard	2	1	..	..	1	..	..
Oat	26	23	..	..	..	1	2
Peach*	4	3	..	..	1*	..	1
Peanut	3	2	..	..	..	1	..
Pear	5	4	..	..	..	..	1
Pineapple	2	1	..	..	..	1	..
Plum	3	2	..	..	..	..	1
Potato	25	21	..	..	1	..	3
Raspberry	2	1	..	..	..	..	1
Rice	22	21	..	..	..	1	..
Rye	17	15	..	..	..	1	1
Shad	2	1	..	..	..	1	..
Spinach	13	12	..	..	..	..	1
Turnip	6	5	..	..	..	..	1
Turkey	3	1	..	..	..	..	2
Wheat, whole	29	23	..	..	..	4	2
Wheat, leucosin	5	3	..	..	..	1	1
Bacteria							
Staphylococcus pyogenes aureus	2	1	..	..	..	..	1
Staphylococcus pyogenes albus	2	1	..	..	..	..	1
Staphylococcus pyogenes citreus	2	1	..	..	..	..	1
Remainder all neg.							
Animal Emanations							
Goose feathers	4	3	..	..	..	..	1
Horse dander	5	4	..	..	..	..	1
Horse serum	4	3	..	..	..	..	1
Total			1	3	17	25	51

* In one case the stock peach protein was found doubtful (±), but when a sample of some fresh, home-cooked peaches was tried, the reaction was 2+.

TABLE 5.—Summary of the Results of the Skin Tests—Asthma Cases

Proteins	Cases	Neg.	4+	3+	2+	1+	±
Almond	25	24	..	..	..	..	1
Banana	30	27	..	..	1	..	2
Barley	30	29	..	..	..	..	1
Bean	25	24	..	..	..	..	1
Beef	28	24	..	..	3	..	1
Blackberry	24	23	..	..	..	..	1
Bluefish	24	23	..	1	..	..	..
Buckwheat	24	23	..	..	..	..	1
Cabbage	24	22	..	..	..	..	2
Carrot	26	24	..	..	..	1	1
Cauliflower	24	23	..	..	..	..	1
Celery	23	22	..	..	..	1	..
Cheese	24	22	..	..	..	1	1
Chicken	29	26	..	1	1	1	..
Clam*	23	22	..	..	..	..	1
Cocoa	24	22	..	..	..	..	2
Codfish	26	25	1	..	..	..	..
Coffee	27	24	..	..	..	1	2
Corn	25	24	..	..	..	..	1
Duck	26	22	..	..	1	1	2
Ovomucoid	17	14	2	1	..	..	..
Egg, white	16	12	..	3	..	1	..
Egg, whole	28	25	..	1	2	..	..
Egg, yolk	16	12	..	2	..	2	..
Fig	25	20	..	..	..	..	5
Goose	25	21	..	..	1	1	2
Grapefruit	25	24	..	..	..	..	1
Guinea fowl	19	17	..	..	1	1	..
Haddock	23	21	1	..	..	..	1
Herring	25	24	..	1	..	..	..
Lactalbumin	18	15	..	..	2	..	1
Lamb	28	25	..	..	1	2	..
Lentil	25	24	..	..	1	..	..
Mackerel	22	21	..	..	1	..	..
Milk (cow's)	30	27	..	..	..	2	1
Milk (goat's)	2	1	..	..	1	..	..
Milk (Dryco)	2	1	..	..	..	..	1
Mustard	27	24	..	2	..	1	..
Oat	29	26	..	..	..	..	3
Onion	29	26	..	..	..	..	3
Oyster*	22	21	..	..	..	1	..
Parsnip	23	22	..	..	..	..	1
Pea	27	26	..	..	..	1	..
Peach	26	25	..	..	..	..	1
Pear	26	23	..	..	..	1	2
Perch	22	20	..	..	..	1	1
Pike	23	22	..	1	..	..	..
Pineapple	15	14	..	..	..	1	..
Pork	25	24	..	..	..	..	1
Potato	30	27	..	..	1	1	1
Radish	24	23	..	..	..	..	1
Rice	30	29	..	..	..	..	1
Rye	30	29	..	..	..	..	1
Salmon	22	21	..	..	1	..	..
Shad	22	21	1	..	..	..	..
Sole	21	20	..	1	..	..	..
Squab	23	21	..	..	..	..	2
Squash	24	19	..	..	..	..	5
Turnip	23	22	..	..	..	..	1
Turkey	23	20	..	..	..	1	2
Veal	24	21	..	..	..	2	1
Wheat (whole)	30	29	..	..	..	..	1
Wheat (globulin)	9	8	..	..	..	..	1
Bacteria							
Staphylococcus pyogenes aureus	26	25	..	..	..	..	1
Staphylococcus pyogenes albus	26	25	..	..	..	..	1
Diphtheroid bacillus	26	24	..	..	..	..	2
Remainder all neg.							
Animal Emanations							
Cat hair	28	22	..	..	..	2	4
Dog hair	26	20	..	..	..	2	4
Chicken feathers	29	22	..	..	1	3	3
Goose feathers	29	22	..	..	..	3	4
Sheep wool	27	25	..	..	..	..	2
Horse dander	29	22	..	..	1	2	4
Rabbit hair	22	14	1	5	1	..	1
Pollens† (31 in all)	13	8	..	..	2	1	8
Total‡			6	19	21	37	88

* Interesting to note that these were negative in a case with general fish sensitization, but who had never been offered any variety of sea food.

† All negative except 2+ to corn pollen and short ragweed; 1+ to corn pollen, and ± to corn pollen (3), cherry, clover, locust, oak, and rye (1 each).

‡ Pollens not included in totals.

The Proteins Most Frequently Giving Positive and Doubtful Reactions.—An analysis of the frequency with which the various proteins give definitely positive reactions (without regard for the doubtful ones), will probably give the truest estimation of their relative places as causative factors in allergic syndromes. Table 6 has been prepared on this basis. Positive reactions were most commonly secured, in the cases of bronchial asthma with the proteins of rabbit hair, egg (both white and yolk), chicken feathers, lactalbumin, beef, lamb, mustard,

TABLE 6.—THE PROTEINS MOST COMMONLY GIVING POSITIVE REACTIONS—IN THEIR ORDER OF FREQUENCY

No.	Proteins	No. of Cases Tested	Per Cent. of Positives	No.	Proteins	No. of Cases Tested	Per Cent. of Positives
			Asthma Cases (31)				
1.	Rabbit hair	22	33	15.	Dog hair	26	8
2.	Egg-white	16	25	16.	Duck	26	8
3.	Egg yolk	16	25	17.	Goose	25	8
4.	Ovomucoid	17	18	18.	Veal	24	8
5.	Chicken feathers	29	14	19.	Cat hair	28	7
6.	Lactalbumin	18	11	20.	Cow's milk	30	7
7.	Beef	28	11	21.	Potato	30	7
8.	Egg, whole	28	11	22.	Turkey	23	4.5
9.	Lamb	28	11	23.	Celery	23	4.5
10.	Mustard	27	11	24.	Pear	26	4
11.	Horse dander	29	10	25.	Coffee	27	4
12.	Goose feathers	29	10	26.	Carrot	27	3.5
13.	Chicken	29	10	27.	Banana	30	3
14.	Guinea fowl	19	10				
			Eczema Cases (30)				
1.	Ovomucoid	6	50	10.	Bean	7	14
2.	Egg-white	13	38	11.	Banana	9	11
3.	Egg, whole	28	32	12.	Lamb	12	8
4.	Lactalbumin	7	28	13.	Chicken	15	7
5.	Egg yolk	15	20	14.	Rye	17	6
6.	Lima bean	6	16	15.	Rice	22	4.5
7.	Corn	7	14	16.	Barley	24	4
8.	Whole wheat	29	14	17.	Potato	25	4
9.	Cow's milk	29	14	18.	Oat	26	4
			Both Asthma and Eczema Cases (61)				
1.	Egg-white	29	31	13.	Goose feathers	33	9
2.	Rabbit hair	24	29	14.	Horse dander	34	9
3.	Ovomucoid	23	26	15.	Beef	36	8.3
4.	Egg yolk	31	22.6	16.	Shad	24	8.3
5.	Egg, whole	56	21.5	17.	Goose	29	7
6.	Lactalbumin	25	16	18.	Duck	30	7
7.	Mustard	29	14	19.	Veal	28	7
8.	Chicken feathers	33	12	20.	Dog hair	28	7
9.	Cow's milk	59	10	21.	Whole wheat	59	6.8
10.	Lamb	40	10	22.	Cat hair	33	6
11.	Guinea fowl	21	9.5	23.	Potato	55	5.5
12.	Chicken	44	9				

horse dander, goose feathers, and chicken. In the eczema group the order is egg (both white and yolk), lactalbumin, lima bean, corn, wheat, whole cow's milk, bean, and banana. When we average the findings in all the cases, we find the most common offenders are egg (both white and yolk, with ovomucoid positive in all the cases in which egg white was positive), rabbit hair, cow's milk (more especially the lactalbumin which is very frequently positive where whole milk is only doubtful), mustard, chicken feathers (with goose feathers slightly less often),

lamb, chicken and poultry in general, and so on down the list with horse dander, beef, veal, dog and cat hair, whole wheat, and potato following.

It is of interest in this connection to note the findings of Baker working with children having anaphylactic symptoms. He found the order of frequency of sensitization to foods to be oats, potato, eggs, pea, rice, casein, beef juice and chicken. This is quite at variance with my figures in so far as I only found one positive reaction in fifty-five children tested out with oats, three positive in fifty-five tested with potato, one in forty for peas, one in fifty-two for rice, and no positives and only two doubtful in twenty-two tested out with casein.

When, however, the number of doubtful reactions secured are combined with the number of positives, a somewhat different order is found.

(a) In the asthmatic cases: Rabbit hair, egg, chicken feathers, goose feathers, horse dander, dog hair, cat hair, fig, lactalbumin, duck, goose, beef.

(b) In the eczema cases: Egg, lactalbumin, corn, chicken, barley, wheat, casein, lima bean, potato, whole cow's milk, bean, beef.

In comparing the findings of various authors, as to the proteins to which children are most commonly sensitized, one sees that egg ranks very high in all the reports. The sensitization to milk is also very common. Although potato was found frequently by O'Keefe and Baker and fairly often by Walker (all ages), I did not find it nearly as often as I did other proteins. The same is true of casein, to which only two children were sensitive (two infants who gave a doubtful reaction to casein with a 2+ reaction to lactalbumin).

It is very interesting to note that the animal epidermal proteins give such a high percentage of positives and are so frequently one of the main etiologic factors in the asthmas of children. Walker[7] found a similarly high percentage in studying adults and children. He reports 17 per cent. positive to horse dander, as compared to 10 per cent. in my series. His figures for feathers were much lower, being only 0.75 per cent., whereas I found 14 per cent. positive.

A very recent finding, and one of apparently great interest to those of us who see cases of hypersensitiveness, is the very large percentage of children who show a sensitization to rabbit hair. Dr. Samuel Bell of New York City last year reported[8] a case of bronchial asthma in a girl of about eight years whose skin reaction to rabbit hair was markedly positive and whose symptoms cleared up almost at once upon the removal of a "felt" tam-o-shanter hat proven to be made partly of

7. Walker: Arch. Int. Med. **22**:466 (Oct.) 1918.

8. Bell: Tri-City Meeting of the Pediatric Section of the New York Academy of Medicine, Dec. 5, 1921.

rabbit hair. He has informed me [9] that he has observed approximately 36 per cent. of positives to rabbit hair among his cases of bronchial asthma in children. Dr. A. Bret Ratner, working separately in my class at the New York Nursery and Child's Hospital Outpatient Department, has found eight positive cases of rabbit hair sensitization, and has reported six of them [10] along with one of my own, whose case history is given below. Working at the same time, I was able to find seven of the thirty-one asthmatics here reported definitely sensitive to rabbit hair, and to relieve four of them almost completely, two of them noticeably, and one but slightly, by removing the offending objects wherever possible. I refrain from using the word "cured" in the first four cases because I feel that no case should be reported cured which has not been absolutely without symptoms for a period of at least six to twelve months, and preferably longer. A positive reaction does not mean immediate cessation of symptoms upon the removal of the offending objects made with rabbit hair, because, as in some of the cases mentioned above, a multiple sensitization is often present and the additional factors in each case must be ruled out. The good result mentioned by Ratner was only secured by first completely eliminating all other causes. It will be instructive to insert here a detailed record of this case as an example of the multiplicity of causes sometimes found.

CASE 1.—Jan. 10, 1921, a Russian Jewish boy, aged 9½ years, was sent to me from the dispensary of another hospital for skin tests and treatment.

Family History.—His family history was entirely irrelevant, except for the fact that his mother was suffering from chronic pulmonary tuberculosis.

Personal History.—He had had measles and chickenpox and a convulsion of unknown etiology at 3 years of age. Between 5 and 6, he had several attacks of urticaria accompanied by nausea and vomiting, and during this time there appeared an eczema on the face, arms, chest and back, which condition was still present, though very mild at the time when he first applied for treatment for his asthma. At 8½ years he had a severe attack of bronchitis and from then on began to get frequent attacks of a typically asthmatic character. He had had his tonsils and adenoids removed with marked relief all summer. During the fall and winter of 1920, however, he had had several "head-colds," each of which seemed to induce a fresh attack of asthma. These attacks would come on about every three weeks, last from two to three days and go away, leaving him absolutely free in the interim except for a nasal congestion. His mother was questioned closely and assured me that he used a feather mattress, a feather pillow, and a feather quilt of which she brought me specimens. He drank much milk, ate a general diet, but was usually very constipated.

Examination.—His physical examination was irrelevant, except for a nasal obstruction, a mild eczema of the face and chest, and the usual lung findings during an attack only. A Wassermann test was negative.

A roentgen-ray examination of his lungs showed nothing save a slight hilus fibrosis.

His V. Pirquet test gave a faintly positive reaction.

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9. Personal communication.

10. M. Clin. N. America **5**:1129, 1922.

Jan. 19, 1921, he was first tested out by the cutaneous skin test and the following positive reactions were found: Lactalbumin, two plus; beef, two plus; goat's milk, two plus; cow's milk, one plus; lamb, one plus; veal, one plus; Dryco Dried Milk, plus minus; squash and perch were doubtful, while human milk and casein were negative, as were all the other tests done at that time.

Treatment.—After observing him for about a month on a so-called milk-free diet which was not very rigidly held to, his relief was so slight that hypodermic desensitization was decided on and begun February 28, on which day his tests were repeated. This time he gave a two plus reaction to a 1:100 dilution of cow's milk. A dilution of 1:400 of lactalbumin gave a definite one plus reaction. His first injection was 0.2 c.c. of a 1:5,000 dilution of whole cow's milk to which he gave a negative skin test. He received injections every four or five days up to May 13, a period of two and a half months, during which time he had had but one short, very slight attack. His skin condition, while at first aggravated by these injections, later cleared up entirely. April 1 lactalbumin gave only a positive (one plus) reaction and April 12 whole milk gave a doubtful reaction, the 1:100 dilution being almost negative. On this day he was tested out for the first time to rabbit hair and showed a three plus reaction. This was considered significant and the mother was asked to bring in samples of the materials with which his mattress, pillow and quilt were stuffed. This she did, but no rabbit hair was among them. She was told to eliminate from the home all articles which could possibly be made with rabbit hair.

May 13, following the injection of 0.5 c.c. of a 1:500 dilution of cow's milk, the patient developed a very severe attack of asthma lasting several days. It was decided to continue the desensitization more slowly and by mouth. This was done and the dose was increased under careful supervision. He had had no attacks during all this time save the one reaction. He went to the country July 5 and, while away, had an attack lasting two days. On his return, his desensitization had progressed so far that he was taking one glass of whole milk daily. August 16 his skin rash returned and was quite troublesome until the milk was boiled and the amount temporarily diminished, when the skin cleared up. September 27, he developed a severe attack of asthma following an ordinary cold. He was found to have a definite nasal and postnasal infection with a catarrhal otitis media. He was then taking one pint of milk daily. Because of a definite nasal obstruction and some tenderness over the right maxillary antrum, he was sent to a nose and throat specialist who reported a definite clouding of the ethmoid cells and of the right maxillary antrum, with a large polypoid degeneration of the right middle turbinate. This was obstructing proper drainage and breathing. It was considered inadvisable to wash out the sinuses in so youthful a patient, but, in the last week of October, the polypoid degeneration was removed under novocain. During the next week he had such a severe attack of asthma (from the lighting up of the sinusitis?) that he had to receive adrenalin hypodermically.

He had several slight attacks during the next month, but December 6 I saw him in such a severe attack that he had to be admitted to the hospital at once, where he was only relieved by morphin after several injections of epinephrin had failed to relieve. While in the hospital, Dr. Ratner's attention was called to this case and he visited the home in a search for rabbit hair. The boy's quilt—one that had been added recently on top of his ordinary coverings—was found to contain rabbit hair and was gotten rid of. From December 25 to the end of January (1922), the boy was in the country. He has since returned to his home. He has had only one attack since his return home and that one very mild. He is at present drinking one quart of milk daily with no bad effect. His skin is clear. His sinuses were examined early in February and were found to have cleared up almost entirely. His skin tests have become completely negative to milk.

This boy illustrates well the complexity of many of these cases. There seems to be little doubt here of the combined etiology—milk and rabbit hair sensitizations plus an additional focal infection. Of course, it is entirely too early to state whether he will remain well, but he is nevertheless markedly improved at the present time.

This case is more or less typical of the majority of the cases one meets. It is rare to find a single etiologic factor (Case 3), but very common to have many factors playing their parts in the causation of the symptoms. In the classification which follows the frequency of secondary infection and focal infection is striking.

CLASSIFICATION OF CASES INTO GROUPS, WITH THE AID OF THE CUTANEOUS TEST, AND THE RESULTS SECURED IN EACH GROUP

BRONCHIAL ASTHMA

1. SENSITIVE: (17)—(*A*) To food alone—4 cases. (1 to eggs, fish, and meat—improved; 1 to eggs, chicken, and poultry, etc.—markedly improved; 1 to mustard alone—cured; 1 to eggs and potato—cured.)

(*B*) To food plus a tuberculous infection—1 case. (Marked sensitization to eggs; given a short series of hypodermic injections to egg before sending to an institution for tuberculosis—now much improved.)

(*C*) To food plus a tuberculosis with a secondary infection in addition—1 case. Sensitive to meats (especially to beef); (permission to send away refused—unimproved.)

(*D*) To food plus animal epidermal proteins—2 cases. (1 to mustard, rabbit hair, lactalbumin and cheese—somewhat improved; 1 to rabbit hair, coffee, and less so to horse dander, wheat and squash—improved slightly [co-operation poor].)

(*E*) To food plus animal epidermal proteins with a secondary infection in addition—2 cases. (1—the case cited above—sensitive to rabbit hair, milk, meats, plus a nasal sinus infection—marked improvement—too recent to call cured as yet; 1 to horse dander, pineapple, carrots and oats, plus badly diseased tonsils—marked improvement.)

(*F*) To pollen proteins—1 case. To corn pollen—cured of both seasonal urticaria and all-year asthma by hypodermic treatment.

(*G*) To animal epidermal proteins with a secondary infection—6 cases, 4 of these to rabbit hair plus a focal infection which required treatment—1 cured; 2 marked improvement, and 1 improved somewhat; 1 was sensitive to chicken feathers and goose feathers, and had badly diseased tonsils and adenoids—cured; 1 reacted positively to an

extract of the dust from his bedroom, and also to chicken feathers and goose feathers and dog hair, plus in addition badly diseased tonsils—marked improvement.

2. NONSENSITIVE: (14)—(*A*) Tuberculosis (pulmonary) was the sole cause in one case, now free of asthma. The tuberculous lesion is disappearing.

(*B*) Specific etiology undetermined in one case cured by change of residence to another part of the city. Attacks recur when he returns to his downtown home. No sensitizations.

(*C*) Purely focal infections—12 cases, 6 cured; 2 markedly improved; 3 moderately improved, and 1 unimproved because focus remains, due to the fact that permission to have badly diseased tonsils removed was refused. (Vaccine gave temporary improvement.)

ECZEMA CASES

1. SENSITIVE: (17)—(*A*) To food alone—11 cases; 5 cured; 3 well (passive desensitization); 2 marked improvement, and 1 somewhat improved.

(*B*) To food and pollen proteins—1 case of multiple food sensitization (egg being the main offender) plus a sensitization to short ragweed—markedly improved.

(*C*) To food with definitely wrong habits of feeding in addition—5 cases; 1 case cured; 2 marked improvement; 1 somewhat improved (very recent), and 1 unimproved when last seen.

2. NONSENSITIVE: (13)—Due to wrong habits of feeding (frequent, numerous feedings or over-feeding as to type of food or both) or in some of the cases to local irritations—13 cases; 5 cases cured; 5 markedly improved under treatment; 1 moderately improved, and 2 cases unimproved with etiology undetermined.

It will be noticed that among the asthma cases there are twelve patients who were cured, eight markedly improved with only a rare, mild attack, or in two no attacks but too recent to report as cured, seven somewhat improved having much less frequent and more mild attacks than before treatment, one but slightly improved, and two unimproved. There were, therefore, 39 per cent. cured and 26 per cent. very markedly improved. Only three cases, or 10 per cent., fall into the class which were not benefited.

The results in the eczema cases are not claimed to be due only to the skin tests, for children of this type tend to get well without any treatment over such a period of time as these were under observation. But I do feel that the improvement was in most cases exceptionally rapid and especially in those with a determinable sensitization to a protein which could readily be eliminated. Recurrences were also rare

because of the warnings given the mothers as to the sensitization. No cases of skin sensitization to any of the bacterial proteins were found in this series of cases.

DISCUSSION

The greatest difficulty met with in studying cases of asthma and eczema is in properly evaluating the various etiologic factors in each person. It is rare to find a single cause, the elimination of which stops all symptoms at once. Such a case, however, is that of the girl (Case 3) who was very sensitive to mustard alone and who has never had an attack of asthma, urticaria, or "biliousness" since the removal of mustard from her diet more than a year and a half ago. Usually, however, there is a multiple etiology with sensitizations to several foods, or animal emanations or pollens. Occasionally, a sensitization is combined with an infectious condition such as a tuberculous process in the chest, or a focal infection with a secondary invading organism. Removing only one or two of these factors will at times give marked relief, but again one must search elsewhere and eliminate all other causes as well. Rabbit hair sensitization is a common cause of bronchial asthma in children. A hypersensitiveness to eggs, milk, mustard or feathers is also frequent.

In treating these cases by means of oral or hypodermic desensitization, the cutaneous tests are of great help as a guide in the progress of the desensitization.

Some important points in regard to the cutaneous test, which have been mentioned in the literature before, are the following:

1. *The Relative Specificity of the Reactions.*—The cutaneous test is not absolutely specific but relatively so. For example, in almost every case in which a strongly positive reaction to egg was secured, there was also a positive reaction, although usually less marked, to chicken and to the poultry group of proteins, and occasionally even to chicken feathers. Moreover, when desensitization is being attempted, it is usually to be observed that not only does the skin reaction to the protein being injected grow smaller gradually, but also the reactions to the closely related proteins.

2. *The State of Anti-Anaphylaxis or Temporary Desensitization.*—A negative reaction is not always final because of this phenomenon. A hypersensitive individual may be in this state for a variable period following exposure to a large amount of the offending protein which gave rise to the usual symptoms. One must guard against this as much as possible by not performing the tests for a reasonable interval after the last attack, and also by repeating the tests wherever possible at a later date.

3. *The Occasional Lack of Correspondence Between Skin Reactions and Clinical Findings.*—(*a*) Quite infrequently one finds a case (Case 12 after receiving treatment) in which the skin reaction is positive without any symptoms appearing upon exposure to the protein. These cases must be considered as potential sensitizations. It is probable that very large amounts of the protein would bring out some manifestations of the hypersensitiveness. This seems quite possible when we remember that there seems to be no relationship between the size of the skin reaction and the severity of the symptoms.

(*b*) Repeatedly negative skin reactions are sometimes found in a case where there is a definite clinical food idiosyncrasy. Though rare, this condition has been observed (Schloss[9]) especially in infants where it is most frequently manifested by gastro-intestinal symptoms brought on by a food, very often cow's milk, to which the skin shows no sensitization. This is believed to be due to a lack of skin sensitization alone.

4. *The Presence of a Highly Sensitive Skin.*—The skin tests are of no use where a positive control test is always present. Certain persons are known to possess extremely sensitive skin (factitious urticaria). This condition makes the interpretation in these cases very difficult if not impossible. It must be remembered, however, that a skin reaction in order to be positive, must have the typical formation of pseudopod-like processes extending out from the wheal. A wheal in which there are no such processes must be considered negative even in the presence of a definitely negative control.

SUMMARY

1. Thirty-one cases of bronchial asthma in children from 1 to 14 years of age, and thirty cases of eczema in children from 5 weeks to 7 years of age are described and studied.

2. The standards used in the interpretation of the cutaneous reactions are set down.

3. A total of 4,520 tests were performed, 979 of these being tests with the same proteins repeated. An average per patient of ninety-six different proteins (with twenty-eight repeated) were tried on the asthmatic group, and twenty-two different proteins (with five repeated) on the eczema group.

4. There is a much greater incidence of protein sensitizations in children with asthma and eczema than in normal children.

5. Approximately one in every twenty-eight or twenty-nine tests performed gave a positive reaction, and one in every eleven or twelve tests was either positive or doubtful.

6. As many as fourteen of the asthma cases and thirteen of the eczema cases gave no indication of hypersensitiveness as determined by skin tests.

7. The proteins of egg, rabbit hair, cow's milk (especially the lactalbumin portion), mustard, chicken feathers and goose feathers, lamb, chicken, goose and duck, gave the most frequent positive reactions.

8. A classification is given of the individual cases into sensitive and nonsensitive, and further into subgroups according to the type of proteins to which they were sensitive (i. e., whether food, animal epidermal, pollen, or bacterial), with the results secured in each subgroup. No cases were bacteria sensitive.

9. The importance of focal infections as an etiologic factor in these children is stressed.

10. Sensitization to the proteins of rabbit hair, which is very commonly found in all homes, is a frequent occurrence.

11. The multiplicity of causes with the consequent necessity of intense individual study is very striking.

12. Occasional findings which limit the usefulness of the protein sensitization test are mentioned.

REPORT OF ADDITIONAL CASES

ASTHMA

CASE 2.—M. R., a Jewish boy, aged 3 years, had suffered from asthma since 1 year old. His mother remembered that she had had eczema in her childhood. Eggs, beef juice, or any kind of fish made the boy "deathly" sick, with nausea, vomiting, hives, and asthma. He was brought to the hospital for relief from the more or less continuous asthma and wheezing respirations. He had in addition a chronic nasal discharge, and a mild papular eczema of the face, chest, and back. Skin tests showed a marked sensitization to very many foods, among them eggs, chicken, poultry, all fish (except lobster and oyster, which he had never eaten), banana, beef, pears, etc. Limitation of diet was naturally a very difficult procedure, and was never properly carried out because of a continued loss of weight, to which the mother objected. She preferred that he suffer from the mild attacks of asthma rather than lose weight on a very rigid diet. Hypodermic desensitization to egg-white was started but not continued very long because of the further objection on the part of the mother to this method. These few treatments, however, caused the cessation of the nasal discharge. At the same time, his eczema cleared up entirely, and his asthmatic attacks were exceptionally mild during this period. He is at present in better condition than ever before because the mother is able to control his diet fairly intelligently with her knowledge of his sensitizations.

CASE 3.—J. W., a girl, aged 12 years, suffered with attacks of asthma since 10 years old. She would have an attack about every third month. It was usually quite severe, coming on with vomiting and accompanied by crops of hives. She knew that delicatessen foods always seemed to make her sick. Her skin tests showed a strongly positive reaction to mustard and a doubtful one to oats. Put on a diet free of these two articles, she had no attack for the following six months. Dec. 22, 1920, at my request, she took a minute amount of mustard with her usual midday meal. As expected, this brought on a typical severe attack which lasted for almost a week. Since then over a year has elapsed with not a sign of any asthma. Her skin tests have remained unchanged.

CASE 4.—A. Y., a Greek boy, aged 9 years, had had asthma since 5 years old. In the spring of 1920, when in this country only a few months, he developed pneumonia and empyema for which he was operated on at Mt. Sinai Hospital. Tuberculosis was at this time suspected. He came under my observation in November, 1920. His asthma was quite severe. There was a definite family history of both asthma and eczema on the paternal side. Eggs were said to cause the patient to become nauseated and vomit. He had generally enlarged lymph nodes, an enlarged liver and residual physical signs in his chest. A Pirquet test was markedly positive. Roentgenograms of the lungs showed definite areas of calcification in the enlarged paratracheal and bronchial nodes plus a marked hilus fibrosis and diffuse peribronchial thickening. His skin tests were strongly positive for egg (white and yolk), and chicken and less strongly for duck, goose and guinea fowl. Rigid abstinence from these foods in any form relieved only slightly. He was then given eight injections of egg-white, beginning with 0.1 c.c. of a 1:100,000 dilution (he gave a one plus reaction to the 1:10,000 dilution), and increasing every three or four days by 0.1 c.c. He felt much better during this period, but the eighth injection gave him such a severe general reaction, with typical asthma, that it was considered rather unsafe, with the lung involvement, to proceed further at that time and he was sent away to a tuberculosis hospital. He is improving very slowly but appreciably under a careful regime and dietary. He now gets an attack only at two to three week intervals. They last about twenty-four or thirty-six hours and go away leaving him without the continuous wheezing he formerly had. His skin tests have remained the same.

CASE 5.—M. M., a colored girl, aged 10, who had suffered with asthma since the age of 5, was brought to the clinic by our social service nurse. The child was in such a weak condition that she could hardly stand up. Her dyspnea and orthopnea were extreme. She had a severe, dry, cracked eczema of the arms, chest and legs. Oatmeal was the only food that she was thought to have an idiosyncrasy to. An older sister had had asthma until she had gone South to college at the age of 18. Skin tests on the patient showed a marked sensitization to horse dander with a lesser reaction to pineapple, carrots and oats. On investigation, it was discovered that she lived immediately opposite the stables of Durland's Riding Academy. She was immediately sent to the country, where during six weeks she gained 9 pounds in weight and had no asthma whatsoever. Her skin was absolutely clear on the day she arrived home. That night she began to wheeze and the next day had a severe attack of asthma. Her skin again began to get rough and within a few days was as bad as ever. Injections of dilutions of horse dander were begun and improvement was soon very noticeable. When she was well enough, her tonsils, which were badly diseased, were removed. The skin condition has been held in check but never completely cured. The constant exposure to horse dander emanations continues to bring on attacks, although very mild in comparison. The parents have been unable to move up to the present. She could go to school with regularity soon after the injections had gotten under way and the mother was apparently satisfied to the extent that she did not like to keep the girl out of school for these injections and so they have been discontinued. The attacks come only once in every two to three weeks and are then only mild and last but a few hours.

CASE 6.—M. H., a boy, aged 12, had had urticaria for ten summers and during the past two years had been getting attacks of bronchial asthma. He had had eczema when 1 year old. His skin tests were all negative as to any food sensitization, but he gave a two plus reaction to corn pollen. Injections of increasing doses of corn pollen dilutions (prepared by the Arlington Chemical Company of Yonkers) were given to the patient, in all about ten injections. That summer he had only a very mild attack of urticaria and none at all the following summer (1921). He has had no asthmatic attacks since this treatment was given.

CASE 7.—I. N., a boy, aged 13, had had asthma, the same all year round, since 4 years of age. His attacks came on especially at night. There was

nc history of eczema or urticaria. His father's father and a maternal grand-aunt had asthma. The patient's tonsils and adenoids were very badly diseased. Skin tests revealed a strongly positive reaction to rabbit hair and doubtful reactions to a few easily eliminated foods. A pillow he was using contained rabbit hair and he gave a positive reaction to an alkaline extract of this hair. Removing his tonsils and adenoids and changing his pillow effected an absolute cure. He has had no asthma in the eight months since then, although he had several colds.

CASE 8.—J. W., an Irish boy, aged 3, had been suffering from asthma for fourteen months when he came to the clinic. Six months previously his tonsils and adenoids had been removed and this had given him some relief. He still got attacks every few weeks, sometimes very severe ones. His tests showed a sensitization to both chicken feathers and goose feathers. A feather pillow he was using was discarded and a pine pillow substituted, and since then—a period of fifteen months—he has been entirely free of asthma.

CASE 9.—R. G., a girl, aged 18 months, had suffered with spells of difficult breathing and coughing since 6 months of age. An aunt had pulmonary tuberculosis and had come in contact with the child on occasional visits to the home. Examination revealed typical asthmatic breathing and musical râles, but nothing else. The child's nutrition was excellent. Skin tests showed no sensitizations. A Pirquet test was very strongly positive. Roentgenograms of the chest showed two adjacent areas of infiltration in the right lower lobe, the larger shadow being about the size of a quarter dollar. The child ran a temperature of about 100 to 100.5 F. in the evenings for a few weeks, but under good home care (the mother had been a trained nurse) this disappeared, as did the asthmatic symptoms after a month or so, without any but symptomatic treatment. She has not had a return of the condition in over a year now. Her Pirquet test remains the same. Roentgenograms show the lesions slowly getting smaller, although still present six months ago. The child's robust state of nutrition throughout was very interesting.

ECZEMA CASES

CASE 10.—E. A., a girl, aged 4½ years, had had an eczema since the second week of life. At the onset it was a typical infantile eczema which improved and grew worse from time to time but never cleared up entirely. Since 1 year of age it had become much more aggravated and chronic. It was generalized and the skin became thick and firm. She had been told on many occasions that nothing could be done for it. The family history was not suggestive of any anaphylactic conditions. The mother did not know any foods to which the child might have an idiosyncrasy. The skin looked exactly as does a case of mild ichthyosis, but she had itching which is not usually present in that condition. The dry thickened condition of the skin with the deep furrows and cracks gave her face the appearance of that of an old woman.

A Wassermann test on her blood was negative. Skin tests were performed on her chest and abdomen where the skin was least changed and very many positive reactions were secured with the control test being negative. The following were her reactions: three plus to banana and ovomucoid; two plus to short ragweed, egg-white, potato, bean, lima bean, mustard, and a fresh sample of some home-cooked peaches which were suspected because of a doubtful reaction to the stock preparation of peach; one plus to egg-yolk, pineapple, shad, and egg plant; doubtful reactions were secured to thirteen or fourteen foods, among which were wheat and lactalbumin. The prognosis was naturally poor. As rigid a diet as possible was prescribed and injections of egg-white were begun. The first dose was 0.05 c.c. of a 1:100,000 dilution of egg-white. This dose had to be increased very slowly and carefully because of the itching and aggravation which an increased amount often set up. As the patient lived out of town, the treatments could be given but once a week. The improvement has been very great. Her entire trunk, neck, arms, and thighs are as smooth and soft as most normal children's. She occasionally scratches

her back when an injection has caused itching. Her face has cleared up remarkably. On several occasions in the past two to three months it was absolutely clear and smooth, but then the dry scaliness reappears for a few days—never very marked—and goes away again. The lesions on her hands, forearms, and knees persist more stubbornly but look very much better than at the onset of treatment. For a period of two months, hypodermic treatment was stopped and mouth desensitization was attempted, but with poor results. After this period, the skin reactions to egg-white were as markedly positive as at the beginning of treatment, so that the dose had to be materially cut down again, almost to where we began at first. It is my intention to give her additional injections of ragweed protein this spring to see if improvement will be any more rapid or complete.

CASE 11.—M. C., a female colored child, aged 14 months, had had eczema since her sixth month. Her face, scalp, and buttocks were involved, and the lesions were of the red, moist, exudative variety. The family history was negative as to syphilis or anaphylaxis. Skin tests were all negative. Wassermann and Pirquet tests were negative as was a roentgenogram of the lungs. The mother's Wassermann test was negative. Local treatment helped very slightly. The lesions on the forehead became hypertrophic and assumed a keloid-like appearance. The buttocks cleared up very slowly. When last seen, at 2 years, the eruption on the forehead was still present.

This is the sort of case, I believe, for which roentgen-ray treatment may have done some good. I present it here to show a case in which the skin tests did not help at all.

CASE 12.—A. F., a girl, aged 22 months, had had eczema since four months of age. When first seen it was of a mild, dry seborrheic and papular variety, on the face, arms and buttocks. The mother had had eczema and urticaria in her childhood, and throughout her family were similar histories. Her skin tests gave two plus reactions to eggs and milk, and one plus to rye and wheat leucosin and proteose, with doubtful reactions to corn, barley, oats, potato, and wheat globulin and glutenin, and coffee. Her control test was negative. It is interesting to note that her parents owned a bakery and lived in the rear. A cereal-free diet with only one pint of boiled milk and no eggs was attempted as closely as possible. The child was taken at about this time to live with her grandmother in Long Island City and I did not see her again for a year. She was absolutely free of all eruption which had cleared up fairly rapidly on the diet and while away from home. In the preceding few months her diet had gradually been made more liberal, adding one cereal after another and then foods with egg in them until at the time when I saw her again she was eating almost everything. Her skin tests, at this time, instead of being negative as expected, were the same as they had been. This is an interesting example, in my opinion, of a so-called latent sensitization in which the amount ingested is not enough to give her symptoms. She apparently has become somewhat desensitized so that she may eat ordinary amounts of these foods without the return of the eczema.

CLINICAL DEPARTMENT

A CASE OF MYELOID CHLOROMA*

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Cases of chloroma are sufficiently rare to warrant reports of individual cases, particularly if of the myeloid variety, as the literature shows they are of less frequent occurrence than the lymphatic form.

REPORT OF CASE

History.—K. F., a boy, aged 18 months, the youngest child of three, born of healthy American parents, breast fed, was always well, except for an intestinal indigestion with diarrhea at 10 months, a double otitis media at 14 months, and an acute digestive disturbance at 17 months due to indiscretions in diet.

Aug. 30, 1919, the child was brought to the Clinic because of extreme irritability, restlessness at night, puffiness about the eyes and a swelling which had appeared on the left side of the head between the eye and the ear. Examination showed in addition, an enlarged gland at the angle of the jaw on the left side. There was a slight digestive disturbance.

Sept. 11, 1919, the weight was 10,810 gm., with a ptosis of the lid on both sides (the right worse than the left). A tumor was also manifest for the first time on the glabella and over the right zygomatic process.

September 17, the temperature was normal. The white blood count was 81,600 and the differential count showed 88 per cent. myeloblasts, myelocytes, micromyelocytes and degenerated forms, the remainder of the nucleated cells being a few nucleated red cells, small lymphocytes and polymorphonuclear neutrophils. The Wassermann was negative.

Urine: The urine was repeatedly negative.

At this time a diagnosis of myeloid chloroma was made, based on the blood findings and the tumor formations characteristically found on the calvarium.

Physical Examination.—Sept. 17, 1919. The tumors between the eyes and the ears on both sides have decreased in size somewhat; both softer than when last seen. On the left side it is 3 by 2.5 cm. in size; slightly raised. The right side is a little more prominent, the swelling extending from the eye to the ear, about 3 cm. in vertical diameter. Both eyes are bloodshot. The right eye nearly closed by the "drop" lid. Venules dilated on both sides. A tumor is also found in the right cheek, about the size of a walnut, and somewhat flattened in shape. Another is found on the left cheek, about the size of a hazelnut. There are no other tumors on the head aside from those mentioned. The skin shows ecchymotic spots on the left side of the abdomen; also an ecchymosis in the left cheek, 2 cm. in diameter, said by the parents to have followed an injury; this, however, is doubtful. The abdomen is flaccid. The liver edge 5 cm. below the margin of the ribs, in the right nipple line. The spleen is 2.5 cm. below the margin of the ribs, in the left anterior axillary line. Weight, 11,335 gm. In the right inguinal region there was a group of enlarged lymph glands, collectively about the size of a pigeon's egg.

The day following the child had a convulsion, became comatose, and died. On this day another blood count was taken: 68,400 leukocytes, 2,800,000 erythrocytes, and the hemoglobin 70 per cent.

* Received for publication, Nov. 8, 1921.
* From the Duluth Clinic.

NECROPSY FINDINGS

The necropsy was performed, Sept. 18, 1919, five hours after death.

Macroscopic.—The body was that of a well nourished male infant, 75 cm. in length and weighing 11,300 gm. The head circumference (fronto-occipital) measured 44 cm., the abdominal 47 cm., and the chest 47 cm. The skin was pale and mottled and showed postmortem lividity over the posterior part of the thorax. Rigor mortis was present in moderate degree. The hair was scant and dry. The scalp showed a slight seborrhea sicca. The anterior fontanel was open. The eyelids were swollen and the conjunctivae showed injection and ecchymosis, which was more marked on the right.

There was a tumor over each zygoma, having a firm consistency and the size of a hazelnut; tumors, somewhat larger in size and of a softer consistency, were present in each cheek, anterior to the parotid glands. Similar tumor masses were also present in the right submaxillary and the right submental regions.

Abdomen: The subcuticular fat was of normal thickness, consistency and color. The peritoneum was smooth, moist and shining. There was no fluid in the abdominal cavity.

The liver was moderately enlarged, the anterior edge being 4 cm. below the costal margin in the midclavicular line. On section it appeared normal in consistency and color. The gallbladder was somewhat thickened. The spleen measured 3 by 5 by 7.5 cm., and on section showed a firm and fairly fibrous surface. There were numerous adhesions between the anterior surface of the stomach and the transverse colon. The omentum immediately around these adhesions was thickened and studded with numerous small nodules. The pancreas was normal in size, but had a consistency somewhat firmer than normal. The left kidney measured 3 by 4 by 4 by 8 cm. The capsule stripped easily, revealing a smooth surface. On section there were found to be numerous small nodules, similar to those seen in the omentum, scattered through the kidney substance. There were also small circumscribed pus pockets in the medulla. The markings were fairly distinct. The right kidney was of the same size and on section revealed a marked pyonephrosis, which had obliterated some of the pyramids. Nodules and pus pockets, similar to those seen in the left kidney, were present in both the cortex and medulla. These varied in size from a pinhead to a hazelnut. The ureters were 1 cm. in diameter and were thickened. Their external surfaces were studded with small nodular tumors. The mesentery was greatly thickened and freely studded with small nodules, the largest approximating the size of a hazelnut. The stomach, intestines and urinary bladder showed no changes.

Thorax: The costochondral articulations were not enlarged but on the inner surface of the right sixth rib near the costochondral articulation was a small tumor measuring 0.75 by 1 by 1 cm. in size. There were no pleural adhesions and the lungs appeared to be normal macroscopically, except for a few airless areas. A large amount of turbid fluid, containing numerous white particles, was in the pericardial cavity. An irregular and lobulated tumor the size of a walnut, was found in the pericardium, extending upward from the diaphragmatic surface. The heart was normal in size and the valves were normal. The myocardium and epicardium contained innumerable small tumors, similar to those found in the kidneys.

Cranium: Section of the scalp showed the muscles to be pale. The scalp was easily removed except over the glabella, where a tumor, 1 by 2.5 by 2.5 cm. in size, and involving the periosteum was found. The anterior fontanel was 2 cm. in diameter. The dura was firmly adherent to the skull cap underneath the tumor and in this region the meninges were slightly thickened, and the brain injected. On section the brain substance appeared to be normal. The choroid plexus showed miliary tumors throughout. The spinal cord was negative.

Microscopic Study.—Microscopic sections of the tumors, taken from different parts of the body, show a more or less constant picture, varying somewhat, dependent on the character of the tissues infiltrated.

Kidneys: The section shows an area of kidney tissue almost entirely replaced by masses of tumor cells. These masses do not have a sharp line of demarcation, as seen in carcinoma, and show no tendency to any definite arrangement, although here and there circular configurations or rows of cells might suggest attempt at aciniformation. The cells are supported by a delicate fibrous network. The cells are practically all mononuclear, varying somewhat in size, and having round, triangular or quadrangular contours. The nuclei are relatively large, occupying one third to one half of the cell area; they are rich in chromatin and deep staining. The cytoplasm takes a rather deep eosin stain. In certain areas cells show degenerative changes, as evidenced by nuclear disintegration. Blood vessels are difficult to identify and simply suggest spaces between the cells. The tubules and some of the glomeruli are atrophied to a slight degree.

Liver: Section shows small masses of tumor cells having the same histologic characteristics and invasive tendencies as those seen in the kidney section. Some of the cells, however, are larger and show evidence of karyolysis.

Heart: The muscle fibers are separated by masses of tumor cells, exactly similar to those described in the kidney section. The invasion of tumor cells is very extensive.

Lungs: Sections through the airless areas, described above, show some of the alveoli filled with serum; while others, especially around the relatively larger arterial branches, contain cells histologically similar to the tumor cells in the kidney. Some of these infiltrate the alveolar walls.

Sections of lymph glands and the tumor masses over the glabella and the zygomatic processes showed pictures exactly similar to those described in the kidney section.

HISTORY AND REVIEW OF LITERATURE

It has always been a mooted question as to whether chloroma and the acute leukemias are definitely related in their pathogenesis, and authorities have aligned themselves on one side or another.

The first description of a case in the literature is by Allen Burns,[1] an American, in 1823. The name "chloroma," however, was first used by King,[2] of Glasgow, in 1853, antedating by one year, Aran[3] who is usually recognized as the author of the name. Aran himself recognized King as the first to use the term, but strangely enough, King does not mention the name "chloroma" in his paper, except in the title, which led Dock to infer that the name was known previous to the publication of King's article, at least in a conversational way. The first comprehensive study of the reported cases was in 1893, by Dock,[4] who collected seventeen cases including his own—but since then reports have been more frequent, and now more than 100 cases have been reported. All the early cases were considered to be of the lymphatic type, and it was not until the twentieth century that the myeloid type was described, when Roman[5] first collected the cases in the literature corresponding to the latter type. A better understanding of hematopoietic function

1. Burns: Observations on the Surgical Anatomy of the Head and Neck. 1823.
2. King: London & Edinburgh Monthly J. M. Sc. **17:** (Aug.) 1853.
3. Aran: Arch. gén. de Méd., October, 1854.
4. Dock: Am. J. M. Sc. **106:**211, 1893.
5. Roman: Beitr. z. path. Anat. u. z. allg. Path. **55:**61.

is probably the reason for this more frequent recognition of the presumably less frequent myeloid form, as since then the proportion of myeloid cases has been fairly large, leading to the assumption that these cases were previously unrecognized, just as we now know that acute myelogenous leukemia is more frequently present than is ordinarily supposed.

Cause and Symptoms with Differential Features.—The symptomatology of the acute leukemias and the chloromas is similar in nearly every regard. Lehndorff [6] mentions the predilection of the tumor growths for the bones of the head and orbit in chloroma as a distinguishing feature of this condition. Practically all observers agree in this, and add as further differential points the distinctive color of the tumors postmortem, except in the fulminating cases. The course, clinical symptomatology, blood picture and termination, are the same. The consensus of opinion is that both are due to primary bone marrow disease, and that the infiltration into the tissues is more extensive in chloroma. The latter is more distinctly heterotopic, and its infiltration into heterotopic tissues is a characteristic. Threadgold [7] considers the infiltration of vessel walls and the surrounding connective tissue typical of chloroma, indicating a greater degree of malignancy.

The differentiation from acute leukemia is not the only obstacle in the diagnosis, as other conditions are frequently simulated. This is true of such clinical entities as lymphosarcoma, Hodgkin's disease, Sternberg's leukosarcomatosis, the so-called "nodular" leukemia and epinephroma. In contrast to lymphosarcoma and Hodgkin's disease, we have the distinctive blood picture, which in these two conditions is never so markedly altered. Gumbel [8] mentions the more marked, regular disposition of the cells in sarcoma as another factor. In Hodgkin's disease there is a slower course, with the absence of involvement of the parenchymal organs of the body and the usually nearly normal blood picture. Of the allied sarcomatous conditions, the disease known as epinephroma simulates chloroma most closely. It is characterized by metastases about the head and face, but is primarily an affection of the suprarenal glands, and the blood picture is aleukemic. Differentiation between leukosarcomatosis, nodular leukemia and chloroma is more difficult, and they probably are all merely variants of acute leukemic processes. Differentiation is made increasingly difficult when we consider the fine lines drawn in the interpretation of the cells found in blood smears. The cell frequently predominating in these cases is the so-called "lymphoid" cell, which resembles very

6. Lehndorff: Jahrb. f. Kinderh. u. phys. Erziehung, July, 1910.
7. Treadgold: Quart. J. M. **1**:239, 1908.
8. Gumbel: Virchows Arch. f. path. Anat. **171**: 1903.

closely the large lymphocytes found in the normal blood. Pappenheim [9] describes a cell of this type as the mother cell of all white blood cells. This cell is normally present in the foetus in the marrow of bone, the spleen, the liver and the lymph glands, but does not persist in adult life. He believes that in fetal life this cell has the power, probably through two varying factors, to develop either into a lymphocyte or a leukocyte.

Ward [10] and other observers conclude that these large cells in the leukemic processes are a reversion to the primitive mother cell, which has this potentiality to form lymphocytes or myelocytes, according to the exciting factors predominating. This unknown factor is the agent which predetermines a myelogenous or a lymphatic type of acute leukemia. This is borne out by the fact that in myeloid chloroma or in acute myelogenous leukemia one finds all graduations from the mother cell to the myeloblast, the myelocyte and, finally, the adult polymorphonuclear cell. Ward claims that the considerations of the tissues affected in the pathology are inadequate grounds for classifying leukemias, as we know that obviously myeloid tissue may be found in the marrow, since these mother cells, by virtue of their presence in lymph glands, may, paradoxical as it may seem, form myelocytes, and in the bone marrow, lymphoyctes. Both sorts of tissue may be found in the tumors of chloroma, one or the other predominating. The clinical course and gross pathology of myeloid or lymphatic chloroma, as in acute leukemia, must, therefore, be solely made from the blood picture and from the microscopic sections of the tissue. When these large lymphoid cells are present in predominating numbers, one cannot conclude that the case is of the lymphatic type merely on account of this finding, and if myelocytes are present to any degree, the diagnosis of the myeloid form of leukemia is proper. The more forcible the stimulus to overproduction of the cells, the more primitive the cell type, and the more difficult the differentiation. We have an analogous response in the erythroblastic formation, produced by varying degrees of hemolysis. Likewise, in carcinoma, at times the parent tissue is reproduced, whereas in more rapidly growing epitheliomas the character of the cells may be of an indifferent type. It must be borne in mind, however, that acute cases, from the beginning, are, during their course, always permanently lymphocytic or myelocytic, and a metamorphosis of the cells does not take place after the process has once begun. In the more slowly progressive cases, the differentiation is less difficult, and aside from the blood findings, sections of the spleen frequently show myeloid cells in the splenic pulp, definitely displacing the lymph adenoid tissue of the malpighian corpuscles.

9. Pappenheim: Folia Hematol., 1904-1909.
10. Ward: Proc. Roy. Soc. Med., Lond. **7**: 1914.

The Winkler-Schultz oxidase reaction is positive in these myeloid cases. Figure 1 shows clearly the predominating type of cells, distinctly myelocytic. Other cells, without granules, are present, undoubtedly myeloblasts and presumably lymphoid cells. The small number of adult cells, both lymphocytic and polymorphonuclear, is striking.

The blood picture in chloroma simulates or is identical with that of acute leukemia. Erythrocytes are oftentimes materially reduced, so that we may have less than one million per cubic millimeter. The hemoglobin is correspondingly reduced. The leukocytes vary in number from a leukopenia, as in Lehndorff's [6] case, he reporting only 5,100, to counts of 300,000 or more per c.m. The acuteness of the process

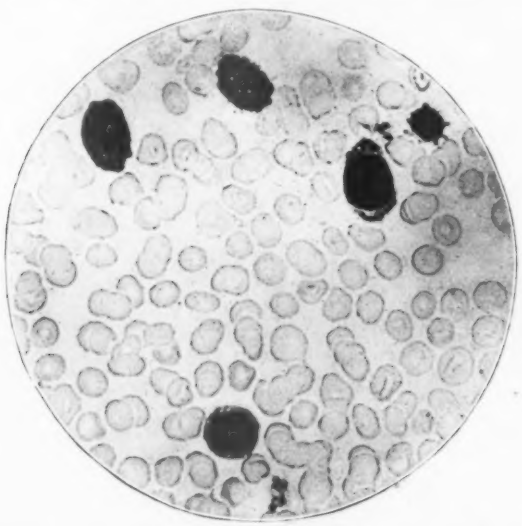

Fig. 1.—Photomicrograph of the blood smear, showing the myelocytes under high magnification.

usually may be identified by the incidence of the large lymphoid cells. The percentage of myelocytes in our case is unusually large. Turk [11] reported 44 per cent. myelocytes, whereas ours showed 77 per cent.

A feature in our case not definitely explicable is the preponderance of myelocytes over the large, indeterminate lymphoid cells, in view of the fact that our patient lived only four weeks—a more rapid course than we have noted in any case previously reported.

Aside from the pathogenesis of the disease, another interesting feature is the green color which is almost invariably found in the chloromatous tumors. Quite a few cases, however, have been reported, in which this green color was not present; for example, those of Birk,[12]

11. Turk: Wien. klin. Wchnschr., 1902.
12. Birk: St. Petersb. med. Wchnschr. **7**:377, 1883.

Leber,[13] Wende,[14] Miller [15] and ours. Observers have noticed that the more fulminating the case the less apt the green color is to be present. As an example, Miller's case is cited, the patient living only three months. Our case ran its course in one-third that time. Furthermore, the green color is oftentimes absent in many of the tumors, and greenish discoloration has been noticed in lymphatic tuberculosis and in ordinary leukemias. The cause of the color is unknown. The color usually does not appear except postmortem, but has been seen at operation. Paviot [16] discovered that the color spontaneously fades on exposure to the air, and reappears when treated with ammonia or peroxide of hydrogen.

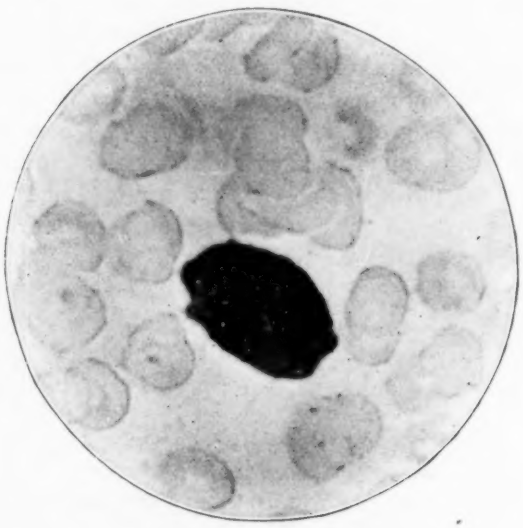

Fig. 2.—Photomicrograph of an individual myelocyte under still higher magnification.

Some of the older theories regarding the distinctive color found in chloroma are those of Balfour,[17] who believed that the pigment was a bilirubin derivative, and of Dittrich,[18] who thought it was a premature putrefactive change. Reynolds [19] thought a combination of fatty acids with iron was the factor. Huber [20] and Chiari [21] believed the pigment to be a lipochrome. They stated that they saw fatty greenish granula-

13. Leber: Arch. f. Ophth. **24**:295.
14. Wende: Am. J. M. Sc., 1901, p. 836.
15. Miller: Arch. Path. Inst., Lond. Hosp. **1**:1.
16. Paviot and Fayolle: Prov. méd., 1897.
17. Balfour: Edinburgh M. & S. J. **43**:319, 1835.
18. Dittrich: Prag. Vierteljahrsschr. f. d. prakt. Heilk. **2**:104, 1846.
19. Pope and Reynolds: Lancet **1**:1351, 1907.
20. Huber: Arch. d. Heilk. **19**: 1878.
21. Chiari: Prag. Ztschr. f. Heilk. **4**: 1883.

tions in chloroma tissue, but the majority of writers have not been able to corroborate this. Askanazy [22] points out the fact that fat is pigmentophil, and thinks that the pigment is merely incorporated in the fat goblets. The parasitic theory has been advanced by Lang, but no one has ever been able to isolate any organisms except such as occasionally are implanted secondarily. Virchow and von Recklinghausen [23] have attributed the color to the so-called parenchyma color typical of chloromatous tumors, just as we have typical parenchyma colors in the liver, myocardium, etc. The color is presumed to be merely due to the physical effect produced by the molecular structures of the tissues. Askanazy [22] promulgated the theory that the color in chloroma is analogous to the color found in pus. He has been able to bring out the same color change in pus as in chloroma by treating it with a mixture of formalin and ammonia. He thinks that cells of the myeloid series are necessary for the production of this green color, as the oxidation of lymphocytes gave no green reaction, except in a case of malignant lymphoma which was found to be rich in eosinophils. He also suggests that the less highly differentiated cells frequently found in the rapidly fulminating cases of chloroma are not so apt to produce this change, myelocytes and myeloblasts causing it more distinctly. This was not the experience in our case; in spite of the high percentage of myelocytes and myeloblasts there was nothing to suggest a greenish tinge, but merely a grayish discoloration. None of these theories has been proved, and a great many are not capable of proof, and the subject is still debatable.

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22. Askanazy: Internat. Clinics, 1913.

23. Von Recklinghausen: Tageblatt der 58ten Versammlung deutscher Naturforscher und Aerzte in Strassburg, 1885.

PROGRESS IN PEDIATRICS

THE ALLERGIC OR HYPERSENSITIVE CONDITION

A REVIEW OF TWO YEARS' PROGRESS *

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An essential advance in the understanding of anaphylaxis and related phenomena, which occurred early in this period of two years, has been the restrictive definition of the term "anaphylaxis." For the classification of the various conditions which were thereby excluded and which had hitherto been regarded as manifestations of anaphylaxis, the terms "allergy" and "hypersensitiveness" are now in general use. The hypersensitive condition, according to Coca,[1] is one of specific or particular reactivity, with characteristic symptoms, to the administration of or contact with, any substance in a quantity which, to most of the individuals of the same species is innocuous. In amplification he adds: (1) "The characteristic symptoms are generally different in the different animal species for the same group of substances." (2) "They are uniform in any one species for various substances." (3) "Where the exciting agent possesses a normal physiological action; for example, the drugs, the symptoms of this action are, with few exceptions, different from those of hypersensitiveness to that agent." This excludes the tuberculin reaction because its symptoms are the same for all species and the so-called "toxin hypersensitiveness" because the symptoms are not different from those of the normal physiological effect of the agent.

The phenomena of true hypersensitiveness, Coca says, are those of anaphylaxis and those of allergy.

Anaphylaxis is defined by the same author as hypersensitiveness induced and experimental, not inheritable, and due to the presence of specific antibodies in certain tissues.

Allergy, on the other hand, is a natural inherited condition of hypersensitiveness which affects only human beings and is not dependent in any way on immunologic antibodies. Coca and other authorities are not, however, in complete accord as to the relation of specific antibodies to allergic phenomena.

Coca points out, furthermore, that if true anaphylaxis ever does occur in man, it does so very rarely, and he believes that there is no positive evidence that it occurs at all in human beings. The allergic

* Received for publication, June 20, 1922.

1. Coca: J. Immunol. **5**:363, 1920.

phenomena to which some of us are subject would, therefore, be independent of artificial sensitization and often, in fact, occur at first contact without opportunity for sensitization to have taken place in the ordinary meaning of the word.

According to Wells[2] the criteria for true anaphylaxis are:

(*a*) The observed toxicity of injected material must depend upon the sensitization of the animal; i. e., must not produce similar symptoms in non-sensitized animals.

(*b*) The symptoms produced must be those characteristic of anaphylactic intoxication, and therefore the same for all antigens with the same test animal, but differing characteristically with each species.

(*c*) It should be possible to demonstrate passive sensitization with the serum of sensitized animals.

(*d*) It should be possible to demonstrate typical reactions in a strip from the virgin guinea-pig uterus.

(*e*) It should be possible to demonstrate amelioration or prevention of the bronchial spasm in guinea-pigs by the proper use of atropin and epinephrin.

(*f*) The possibility that the observed symptoms are caused by capillary thrombosis or embolism must be excluded.

(*g*) After recovery from anaphylactic shock there should be exhibited a condition of desensitization under proper conditions.

Wells also states that there is no satisfactory proof that anything except proteins can act as anaphylactogens (antigens of anaphylactic reactions). The only soluble proteins as yet found not to be antigenic are those which are, from the chemical sense, incomplete proteins, and there is evidence that lack of certain amino-acids may be the essential deficiency. Solubility is essential since, although insoluble proteins may eventually be brought into solution in the animal body, the process is too slow to bring about anaphylactic reactions, and is probably also accompanied by a disintegration of the protein molecule. Heating to a degree that does not disintegrate the proteins affects them only to the extent that it makes them insoluble. Among the few proteins not made insoluble by heating are casein and ovomucoid, and these are antigenic despite boiling.

There is disagreement and doubt as to the true nature of serum disease allergy in relation to anaphylaxis. Drug hypersensitiveness seems undoubtedly a distinct phenomenon. Schloss[3] has been able to transfer sensitization to guinea-pigs by the injection of serum from patients in four cases, and Ramirez[4] reports an interesting case which appears as an example of passive sensitization to horse dander from man to man by transfusion of 600 c.c. of blood. Coca, however, feels that the evidence is not conclusive in this case, that the transfused patient was not already allergic toward dander and has found in addition that the same donor previously gave 800 c.c. of blood to another patient in whom no symptoms of sensitization appeared.

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2. Wells: Physiol. Rev. **1**:44, 1921.
3. Schloss: Am. J. Dis. Child. **19**:433 (June) 1920.
4. Ramirez: J. A. M. A. **73**:589 (Sept. 27) 1919.

Zinsser,[5] in determining the relation of the tuberculin reaction to anaphylaxis, states that in guinea-pigs two fundamentally different types of intradermal reactions can be produced; one immediate and transitory, which develops in animals sensitized against proteins and is true anaphylaxis; and one, the tuberculin type, which develops more slowly, leads to more profound injury of tissues, and is independent of anaphylaxis. Tuberculin sensitization is easily accomplished only with live infections, and reactions follow intradermal injections of extracts of bacteria from which all coagulable proteins, nucleoproteins and Bence-Jones bodies have been removed as far as possible by boiling with acid. Anaphylactic sensitization developed by injections of dead bacterial material is not as quickly developed as tuberculin sensitization. Manifestations of tuberculin sensitiveness also differ in animals and man from those characteristic of anaphylaxis in each species.

Attempting to produce tuberculin sensitiveness with constituents of dead bacteria, Zinsser has obtained hopeful results only with massive injections, and these of substances precipitated with acid.

Fleishner, Meyer and Shaw[6] have shown by experiment that bacterial proteins, whether insoluble or soluble, which sensitize guinea-pigs in an anaphylactic sense will not sensitize its skin. The observations of Auer[7] on the effect of independent local irritants are of interest in this connection. He determined that xylol, when applied to the ears of nonsensitized rabbits, produced no very marked amount of inflammation. If sensitized animals were used, however, the application of this substance, when followed by the injection of otherwise ineffective amounts of the antigen to which the animals were sensitized, caused necrosis. He concluded that this result was due to the accumulation of effective amounts of antigen in the treated area, owing to the inflammatory reaction initiated by the xylol. This suggests a possible relation between drug idiosyncrasy and anaphylaxis.

It does not seem desirable to include in this review references to the literature on anaphylaxis except as they may be directly enlightening to the understanding and treatment of allergy and hypersensitiveness in man. For further information on anaphylaxis one may examine the comprehensive and authoritative treatises by Besredka,[8] Coca[9] and Bordet.[10]

It appears that the nature of anaphylaxis and the understanding of its mechanism is comparatively well established but that the nature

5. Zinsser: J. Exper. M. **34**:495, 1921.
6. Fleishner, Meyer and Shaw: Am. J. Dis. Child. **18**:577 (Dec.) 1919.
7. Auer: Proc. Soc. Exper. Biol. & M. **17**:93, 1919.
8. Besredka: Anaphylaxis and Antianaphylaxis and Experimental Foundations, C. V. Mosby, 1920, p. 156.
9. Coca: Tice, Practice of Medicine, New York, W. Pryor Company, 1920, p. 107.
10. Bordet: Bull. Johns Hopkins Hosp. **32**:269, 1921.

of the allergic or hypersensitive condition in man is more elusive to the understanding and possibly much more complex in its mechanism. As a rule, according to Longcope,[11] the symptoms in man appear early in life and may be observed the first time the patient comes in contact with the substance to which he is hypersensitive. There is undoubtedly a definite tendency toward the inheritance, not of specific hypersensitiveness, but of a quality of tissue that allows of the development of idiosyncrasies. This may be dependent on the condition of the body fluids or of the cells, which permits of a ready union of foreign protein with them. A striking peculiarity of these patients is that the skin reacts by the formation of an urticarial wheal, to the application of the substance or substances to which they are sensitive.

Turnbull [12] believes that sensitization may be acquired during intercurrent disease, or overexertion or worry, or by the absorption of bacterial products from foci, or by over eating or repeated eating of certain foods, or by the ingestion of certain foods too soon after illness or exhaustion. In some persons there may have been a combination of one or more of these circumstances.

The Cutaneous Reaction.—It is remarkable that in contrast to the thousands of cases reported in American medical literature, virtually no activity in the determination of the incidence of the cutaneous reaction is discoverable elsewhere. Furthermore, correspondingly little specific treatment appears to be given. Most foreign reports on the treatment of asthma and of "alimentary anaphylaxis" indicate that the injection or ingestion of peptones or other nonspecific substances is the more favored method.

Either the cutaneous or the intracutaneous method may be used for testing. Schloss [3] in a comparison of the two methods, prefers the cutaneous method. His study was made on 100 infants and children not apparently suffering from disturbances due to food and on thirty who suffered definitely from this cause. His conclusions were that the intracutaneous test is more sensitive but more misleading owing to its tendency to cause pseudoreactions. Many vegetable proteins are difficult to obtain in any form soluble in physiologic sodium chlorid solution, but are soluble only in alkaline solvents and thus cannot be used intradermally. To insure sterility, the proteins used for the intradermal test solutions must be carefully prepared, which adds considerable technical difficulty. On two occasions he has seen severe infections due to such tests. Another objection is that a very sensitive patient may be made seriously ill by the injection of even a minute amount of the protein to which he reacts.

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11. Longcope: J. A. M. A. **77**:1535 (Nov. 12) 1921.
12. Turnbull: Boston M. & S. J. **182**:497, 1920.

The greatest limitations of the cutaneous test, according to Schloss, are that it is not conclusive when negative. This deficiency, he suggests, may be due to lack of skin sensitization, or, possibly to temporary desensitization.

In these opinions Schloss is in agreement with Walker and a large number of other authors; nevertheless there are and have always been those who are vigorous supporters of the intracutaneous method. Larsen, Paddock and Alexander [13] favor the intracutaneous test because it is more delicate; the dry preparations are too uncertain, and they can do more tests in less time and with less trouble. They find, however, that the solutions for the intracutaneous tests are apt to show a precipitate after a while, and lose their potency. They also find that certain points on the body, particularly the fold at the elbow, are more favorable than others to the development of a reaction.

Brown,[14] commenting on Walker's selection of the cutaneous method, questions the value of his experiments with intracutaneous applications because of the use of too much fluid in the injections and because his standard for a normal reaction allowed of too many positive reactions. Using a fluid preparation prepared according to Coca's method in seventy-eight cases, he claims the superiority of the intracutaneous method on the following grounds: (1) every case known to be clinically sensitive to a protein gave a reaction. (2) The scratch method with dry powdered proteins gave positive reactions in only 50 per cent. of the cases, and with his more potent fluid preparations, in only 80 per cent. (3) The intradermal method is not so painful nor so disfiguring. (4) The intradermal method requires less time for application and for obtaining results, which is an important advantage in office work. (5) The same preparation can be used conveniently for treating and testing. (6) General reactions occasionally follow the dermal scratch application as well as the intradermal injection.

Cooke,[15] writing on the danger of constitutional reactions from dermal and intradermal tests, reports one death following an intradermal test injection containing not more than 0.002 mg. of nitrogen. He refers to one instance of constitutional reaction following the scratch method of testing, and reports several in his own experience from the intracutaneous injection. Such cases have been reported by Park [16] and by Gerstenberger and Davis.[17] Cooke suggests that there is special danger of provoking these reactions when changing from a weak preparation to a strong one. When a constitutional

13. Larsen, Paddock and Alexander: J. Immunol. **7**:81, 1922.
14. Brown: J. Immunol. **7**:97, 1922.
15. Cooke: J. Immunol. **7**:119, 1922.
16. Park: Am. J. Dis. Child. **19**:46 (Jan.) 1920.
17. Gerstenberger and Davis: J. A. M. A. **76**:721 (March 12) 1921.

reaction is diagnosed, Cooke recommends, first, the application of a tourniquet to restrict, if possible, the rate of absorption of the injection; secondly, the injection of epinephrin in strong doses—from 0.4 to 0.6 c.c. in children and 1 c.c. in adults, either subcutaneously or intravenously according to the severity of symptoms. This should be repeated after a short interval if symptoms continue to progress and, in his experience, is not dangerous. There may also be indications for the use of strophanthus intravenously, up to 1 mg.

The reports quoted indicate an apparent superiority amounting to about 20 per cent. in favor of the delicacy of the intradermal method of testing, which is or is not offset by the greater liability to constitutional reactions, according to personal opinion. The inference is clear, however, that the protein preparations used by these authors may be especially potent. The method of preparing these proteins was devised by Coca and is explained in his paper on the subject.[18] Vander Veer,[19] testing the comparative potency of four of the best known commercial preparations of proteins, and that obtained from the Department of Applied Immunology of the New York Hospital, known as the "Cornell preparation" (Coca's method), found that none of the commercial preparations even approximated the potency of the strongest Cornell preparation. The strongest or most potent of these seemed about equal in potency to a medium strength Cornell preparation containing 0.005 mg. of nitrogen per c.c. All preparations were in the fluid form and tests were made by the ophthalmic method. They state that experience indicates that for therapeutic effects a maximum potency is desirable but that in using these preparations more caution is necessary in order to avoid constitutional reactions.

Mackenzie and Baldwin,[20] experimenting to determine the exhaustibility of the skin reaction after repeated reactions on the same site, conclude: (1) that in persons manifesting a cutaneous reaction, the reactivity of the skin may be locally abolished by repeated applications to the same area; (2) The reactivity of the skin at the exhausted site may not return for three days or longer. (3) The exhaustion appears to be specific and is not apparent when some other substance is used. (4) The extent of the area of exhaustion is strictly limited to the site of the reaction. (5) Nonspecific cutaneous reactions produced by nonantigenic substances such as histamin are not only inexhaustible but progressively increase with each repetition of the application to the same site. (6) From these results they suggest the possibility of genuine local desensitization and suggest its application in the treatment of hay fever and allergic rhinitis. Larsen, Paddock and Alexander [13]

18. Coca: J. Immunol. **7**:163, 1922.
19. Vander Veer: J. Immunol. **7**:113, 1922.
20. Mackenzie and Baldwin: Arch. Int. Med. **28**:722 (Nov.) 1921.

attempted to confirm these results by repeated injections in two persons at intervals of one hour. With this technic nine intracutaneous injections in one person and four in the other in the same skin area failed to abolish the reaction of the skin. After the eighth injection, the first patient had symptoms of hay-fever, and his eighth and ninth reactions were locally the largest and his arm became much swollen. The next day a typical reaction was obtained again on the same site. When tests were made at intervals of one week, however, these two cases showed a definitely decreased reactivity, the duration of which was not accurately tested, but at the end of three weeks the reaction was again produced as strongly as ever. Their experiments, therefore, are partially confirmatory to those of Mackenzie and Baldwin.

Desensitization and "Hyposensitization".—Cooke,[21] comparing diminished sensitization in allergic conditions in man with desensitization in experimental anaphylaxis, believes that the uniform failure to induce complete insensitiveness in allergy indicates that the relative insensitiveness is of a nature different from that of desensitization in anaphylaxis. He proposes that this distinction he made by designating such a modification of allergic sensitiveness "hyposensitization." He has studied the phenomena of "local exhaustion" of the allergic cutaneous reaction described by MacKenzie and Baldwin, and finds in disagreement with these authors that the exhaustion is nonspecific.

Incidence of the Cutaneous Reaction.—That evidence of sensitization can be obtained by the cutaneous or scratch method in patients whose history is free from the consequences of such sensitization is shown by Baker[22] and by Peshkin and Rost.[23] Baker obtained ten positive and eleven doubtful reactions in twenty-five children whose history indicated no allergic conditions. In comparison with these he reports fifty-five positive and fifty-three doubtful reactions in seventy-four children with symptoms of a probable allergic nature. Peshkin and Rost tested 502 children who were carefully selected as giving in their histories no symptoms which could be attributed to allergy. They report positive reactions in only five, all of whom were more than 5 years of age. They also contained sixty-seven doubtful reactions The total number of tests done on these 502 children was 9,406, an average of only nineteen per patient. Baker concludes that the incidence of sensitization in apparently normal children is almost negligible, but unless his ten positive reactions were all obtained from one or two of his twenty-five normals, one can hardly agree with this estimate. Peshkin and Rost conclude that 10 per cent of apparently normal children show doubtful or positive reactions which decrease as their age

21. Cooke: J. Immunol. **7**:219, 1922.
22. Baker: Am. J. Dis. Child. **19**:114 (Feb.) 1920.
23. Peshkin and Rost: Am. J. Dis. Child. **23**:51 (Jan.) 1922.

increases, indicating progressive desensitization. On the basis of their own figures, especially in consideration of the small average number of tests, this percentage seems too conservative. Baker's tests were confined to food proteins.

The articles of diet found by Baker to be most commonly the source of allergic symptoms were in the order mentioned: oatmeal, potato, egg, peas, rice, casein, beef juice and chicken.

Rackemann [24] reports the results of cutaneous tests in 939 patients presenting various clinical conditions. He obtained positive reactions in about 100 cases in which nothing compatible with this reaction appeared in the history. Subsequently, in following these patients, thirteen developed conditions in relation to which the reaction obtained proved important.

Of 118 cases of hay-fever and pollen asthma, forty-eight gave reactions to proteins other than pollens. Of forty-five cases of horse asthma, fifteen gave positive results with other proteins. Of thirty-one cases of dust asthma, there were many complicating reactions. Of nineteen cases of food asthma, four gave numerous reactions to other proteins. Of 156 bacterial asthmas, 103 with fairly complete skin tests showed positive reactions to other proteins. It is desirable, according to Rackemann, to make a wide variety of tests and to so limit the patients' life and habits that they will come in contact only with negatively reacting proteins. Positive reactions, however, should not be taken very seriously unless compatible with the patient's history, or if further study proves their importance as etiological agents.

Coca [25] states that the age incidence of natural allergies increases rapidly in the early age periods but probably does not greatly exceed 10 per cent. in any period. Coca, Deibert and Menger [26] find that the American Indian is apparently much less frequently affected by the allergies than is the white race.

Sensitization in Hay-Fever.—In this disorder skin sensitization is so nearly universally present that although tests are useful as confirmatory evidence and, as Walker suggests, to determine the strength of immunizing doses, it is, perhaps, more essential to know the usual offending pollens, their regional distribution, and their season of pollination. There are, however, cases in which symptoms are perennial rather than seasonal.

The frequent causes of perennial hay-fever, according to Walker [27] are animal emanations, particularly dander and cat hair, ingested foods, inhaled cereal grains, and sometimes pollens, these last being usually

24. Rackemann: Am. J. M. Sc. **163**:87, 1922.
25. Coca: J. Immunol. **7**:193, 1922.
26. Coca, Deibert and Menger: J. Immunol. **7**:201, 1922.
27. Walker: J. A. M. A. **75**:782 (Sept. 18) 1920.

relieved by the ordinary preseason treatment. Recurring head colds are sometimes due to sensitization which renders the nasal mucous membrane more irritable. Nonsensitive patients with perennial hay-fever, provided there are no demonstrable abnormalities, growths, and the like in the nasal cavities or sinuses, are sometimes benefited or relieved by autogenous vaccines from nasal secretions. A pseudo hay-fever caused by mechanical, thermal or odorific irritants is not uncommon.

Of seasonal hay-fever in New England the dwarf ragweed is practically always the cause of late symptoms—in August and September, and timothy causes 90 per cent of the early cases of hay-fever, in June and July. Rose and redtop occasionally cause early hay-fever and when their season happens unusually early it may interfere with the course of treatment.

Watson and Kibler[28] have investigated the etiology of hay-fever in Arizona and the Southwest. They find that of the wind pollinated flora of these regions the artemisias, or wormwoods, have little, if any, importance. Amaranths are an important factor and their pollen is very active. As a predominating cause of hay-fever in the Southwest they take the place of ragweed in the east and the artemisias in the Rocky Mountains. In some seasons *Atriplex wrightii* will probably take the place of *Amaranthus palmeri*. *Capriola dactylon* (Bermuda grass), causing spring, summer and fall types, will probably prove to be the common grass causing hay-fever at altitudes up to 4,500 feet, and *Poa pratensis* (June grass) above that altitude.

Gaertneria dactylon (rabbit bush) and *Atriplex canescens* (shad scale) are probably the most important plants causing the spring type of hay-fever. Trees are probably not an important cause, but when they do cause hay-fever it will be of a very early type, and the most important are cottonwoods and the ash. The principle of group reactions is not applicable to hay-fever in Arizona and the Southwest.

Heredity in Hay-Fever.—Scheppegrell,[29] investigating the incidence of heredity in 1000 cases of hay-fever, found that 358 patients had relatives of the first degree who also suffered from hay-fever. In view of the heterogeneous nature of the heredity reported in other allergic conditions, the fact that the hypersensitiveness should be manifested in the same way in so many cases seems especially remarkable.

Results and Methods of Treatment of Hay-Fever.—Most of the reported cases of hay-fever have been treated by the preseasonal immunization process of Walker, that is, by the injection of increasing doses of the specific pollen protein, beginning considerably before the season of pollination and being completed shortly previous to the

28. Watson and Kibler: J. A. M. A. **78**:719 (March 11) 1922.
29. Scheppegrell: Med. Rec. **98**:216, 1920.

opening of the season. There is unanimity of opinion that the specific protein must be used in order to obtain success rather than the preparations of mixed pollen proteins distributed by commercial houses.[30] These are open to the same criticism that is justly leveled at mixed vaccines or "shot-gun" drug prescriptions. Scheppegrell [31] finds that some cases do not give a marked skin reaction while others do. In the first group the dose of protein may safely be increased rapidly and it is necessary to reach a much higher number of units in order to be effective. In the strongly reacting group, the dosage should be increased cautiously but treatment should be given as intensively as possible.[32]

In view of reports previously quoted of the greater potency of certain protein solutions, particularly the Cornell preparations of Coca, it seems advisable that all such solutions or dry proteins should be compared with some suitable standard before using.

That treatment during the hay-fever season cannot be given with as much chance of success is indicated by Williams,[33] who reported that twenty-seven cases due to ragweed were not benefited by treatment after the onset of symptoms. Of five cases due to goldenrod, there resulted some benefit in two and much improvement in one. Walker [34] reported, however, that 32 per cent. of twenty-two grass pollen hay-fever patients were made practically free from symptoms by treatment given during the season; 18 per cent. more were benefited to the extent of 75 per cent.; 13 per cent. were 50 per cent benefited; and 13 per cent. were 25 per cent benefited. Of twenty-seven cases due to ragweed, 14 per cent. were made free from symptoms, or practically so; 11 per cent. were 75 per cent. improved; 25 per cent. were 50 per cent benefited, and 44 per cent. were not benefited. He adds that bacterial vaccine treatment during the season occasionally seems to be beneficial. Late preseasonal treatment gives better results than treatment during the season.

Rackemann,[35] reporting the results of preseasonal treatment, found that 9 per cent. of ninety-one patients with fall ragweed hay-fever were made entirely free from symptoms; 62 per cent. were considerably relieved. The best results were obtained by moderate amounts of specific treatment since even after more considerable preparation the tolerance for regweed remained at a very low level. Systemic reactions occur after 2 per cent. of injections and are not always due to an

30. Editorial, J. A. M. A. **77**:791 (March 19) 1921.
31. Scheppegrell: Med. Rec. **100**:191, 1921.
32. Caulfield: J. A. M. A. **76**:1071 (April 16) 1921.
33. Williams: Mil. Surg. **46**:199, 1920.
34. Walker: Arch. Int. Med. **28**:71 (July) 1921.
35. Rackemann: Boston M. & S. J. **182**:295, 1920.

overdose. Hay-fever, he believes, depends on a mechanism which is not anaphylactic, but which is perhaps closely related to that of drug idiosyncrasies.

Walker [34] finds that preseasonal treatment with ragweed pollen was the cause of complete freedom in 22 per cent. of 202 patients; 30 per cent. more were benefited at least 75 per cent.; more than 23 per cent. were only 50 per cent. improved, and 6 per cent. were not benefited at all. Of fifty-two patients whose hay-fever was due to grass pollens, 40 per cent. became free from symptoms; more than 17 per cent. were made practically free; 19 per cent. were 75 per cent. benefited; 17 per cent. were 50 per cent. benefited, and about 6 per cent. were not improved.

For seventy-three patients having ragweed hay-fever who received the preseasonal treatment two years in succession, Walker gives the following figures:

	First Year, Per Cent.	Second Year, Per Cent.
Symptom free	38	16
Practically free	22	22
75 per cent. benefited	19	45
50 per cent. benefited	16	12
Not benefited	6	4

He believes the poorer results obtained the second year in the first group were due to the fact that these patients were apt to get less treatment. He believes that the greater amounts of preseasonal treatment give the better results.

Caulfield,[31] with a small group of thirteen fully treated patients, that is, receiving at least 0.05 c.c. of 1:5 dilution, found that all were very much improved. Walter [36] finds that preseasonal inoculation against ragweed has not helped his cases, while in hay-fever due to rose, timothy, daisy, etc., there has been success. He believes that ragweed hay-fever is a different problem and suggests alkaline therapy and fractional doses of the pollen during the season.

The most interesting divergence from the subcutaneous method of immunizing is that MacKenzie [37] who, having in previous experiments with Baldwin [20] observed the exhaustion of local skin reactivity following repeated applications of specific protein to the same area in a sensitive subject, attempted to exhaust the reactivity of the nasal membranes by the instillation of pollen solutions. He quotes Dsergowsky [38] and Blumenau [39] as producing an active immunity by applications of diphtheria toxin to the mucosa of the nose, throat and trachea, and Ehrlich on the production of immunity by applications of the

36. Walter: J. A. M. A. **75**:670 (Sept. 4) 1920.
37. Mackenzie: J. A. M. A. **78**:787 (March 18) 1922.
38. Dsergowsky: Ztschr. f. Immunol. **2**:602, 1910.
39. Blumenau: Ztschr. f. Immunol. **3**:196, 1911.

antigens ricin and abrin to the upper air passages or to the alimentary tract. He also quotes Sewall and Powell [40] who obtained either sensitization or immunization in guinea-pigs, depending on the dosage, by intranasal instillation.

In his report eight patients were treated by subcutaneous injections only; twenty by local applications only, and twenty by combined methods. His results were:

	Injections	Spray	Both
Complete relief	0	1	3
Almost complete	3	2	9
Considerable	4	6	6
No relief	1	1	2

Although the number of cases was unfortunately very small, the use of the spray in this manner combined with treatment by injections seems attractive.

Sensitization in Asthma.—Unfortunately, the large numbers of cases which Caulfield [31] and Sanford [41] have reported are not so grouped that asthma cases can be separated from those of hay-fever. In Sanford's report 100 cases, presumably asthmatics, reacted to one or more of the proteins derived from foods, particularly to egg white, to which eleven patients reacted. To proteins of various grains, twenty-five persons reacted, and twenty-eight reacted to vegetable proteins, but these twenty-eight were, on the whole, negative to the therapeutic test. Fruits had apparently little to do with his cases of asthma, although banana, which produced several positive reactions, was twice shown to ba a causative agent. In 365 tests with preparations of *Staphylococcus pyogenes aureus* and *S. pyogenes albus* there was not a single reaction. Caulfield also found bacterial skin tests consistently negative and has virtually discarded these proteins in his tests. The experiments, previously mentioned, of Fleishner, Meyer and Shaw are of interest in this connection. Rackemann,[42] however, reports somewhat differently concerning their importance: In forty cases of asthma, he isolated from the sputum 129 different organisms on blood agar. These consisted of: 72 nonhemolytic streptococci, or 60 per cent.; 17 hemolytic streptococci, or 13 per cent.; 17 staphylococcus albus, or 13 per cent.; 7 gram-negative cocci; 5 staphylococcus aureus; 3 pneumococci; 2 gram-negative bacillus; 1 diphtheroid bacilli; 11 others. The percentages, according to Rackemann, would vary with different technic and with mice passages the pneumococci would have been more prominent.

Intradermal tests with proteins from these were done on thirty-nine patients to whom they were autogenous, and twenty-five gave positive

40. Sewall and Powell: J. Exper. Med. **24**:69, 1916.
41. Sanford: Minnesota Med. **3**:180, 1920.
42. Rackemann: J. Immunol. **5**:373, 1920

skin tests. Some gave reactions to heterologous preparations and in all, out of fifty-six patients, thirty-four gave positive reactions.

Treatment was successful in fairly close accordance with the positive tests, ten patients treated with injections of a positively reacting autogenous protein were benefited. It was also true that four out of six treated with positively reacting heterologous preparations were benefited. No negatively reacting patients were improved.

Rackemann concludes that asthma due to bacteria depends on a condition of specific cellular sensitiveness, either to the bacteria themselves or to the products of their action in the body. Caulfield, on the other hand, feels that the failure of vaccine therapy is sufficiently marked in contrast to protein therapy to cause one to question that both are etiologic agents acting in a comparable fashion. Cooke [43] questions the specific value of vaccines in allergy and has failed to find proof that bacterial extracts will act as allergens. He, therefore, does not make the diagnosis of bacterial asthma. For some of these cases he believes that dusts are responsible, and names particularly hay dust and house dust as containing specific nitrogenous factors.

Coke [44] mentions, among other interesting instances of sensitization, certain married patients who are hypersensitive to human hair and whose health is better when sleeping apart. This author, using the scratch tests for diagnosis, finds that 50 per cent. of all asthmatics and 90 per cent. of asthmatic children give reactions. These percentages seem very high in consideration of the extensive reports by American authors. He also concludes that much can be done for nonreacting cases by nonspecific protein therapy.

Pines [45] reviewing 150 cases of asthma, concludes that it is due to protein sensitization and that it is possible with cutaneous tests to determine the etiology in about 50 per cent. of the cases. Cunningham [46] tested thirty-six children with asthma, found positive reactions in eleven, or 30 per cent., but was able to confirm this relationship in only six, or 17 per cent.

Other Causes of Asthma.—Gerdon [47] discusses his experiences with asthma in fur dye workers. The dyes used were ursol dyes, and derivatives of p-phenyldiamin. There seemed to be a distinct relation between the asthma and exposure to this dye and in addition patients suffered from salivation, edema, diarrhea and exopthalmos. Asthma would sometimes recur at the mere odor of the dye. He believes that the indications in these cases point to sensitization.

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43. Cooke: J. Immunol. **7**:147, 1922.
44. Coke: Brit. M. J. **1**:372, 1921.
45. Pines: California State M. J. **19**:29, 1921.
46. Cunningham: Boston M. & S. J. **186**:876, 1922.
47. Gerdon: Zentralbl. f. Gewerbehygiene **8**:201, 1920.

Sluder [48] considers that in some cases asthma may be the result of a nasal reflex and mentions six examples. Knapp [49] believes the disease to be due to insufficiency of the pylorus with long continued pressure of the diaphragm against the lungs. The remarkable case reported by Ramirez, which was apparently due to passive sensitization by transfusion, has already been mentioned.

Pathology of Asthma.—Kamchorn and Ellis [50] report the necropsy findings in an additional case of death from asthma, making two such cases in their own experience, and review the reports of ten similar cases reported by other observers. They conclude that the histology of the bronchi shows simply acute catarrhal bronchitis and does not explain the course of bronchial asthma. The length of time a person suffers from the disease and the number of attacks he has are apparently without effect on the bronchi (The patient reported on had had asthma all his life). The theory of spasm is favored by these findings. In addition to the bronchial findings the cases showed hypertrophy and dilatation of the heart.

Treatment of Bronchial Asthma.—This may be considered first from the specific standpoint, including the diagnosis of protein sensitization and consequent elimination of the indicated proteins, or the diagnosis of an infectious etiology and treatment by immunization. It is the general opinion, and Caulfield states that the results of elimination of allergic substances surpass in promptitude and completeness the results of other methods of treatment.

Hutcheson and Budd [51] treated ninety asthmatics with autogenous vaccines and by removal of diseased foci. Most of the cases were chronic. In fifty-three, or 75 per cent., either complete freedom from attacks or the longest interval of freedom since the disease began was obtained. In the remainder there was no improvement. Walker has previously reported considerable success from the use of autogenous vaccines. Cunningham [46] obtained relief in seven of twenty children so treated. Rackemann's results from the use of autogenous, positively reacting bacterial proteins has already been mentioned.

Gottlieb [52] reported the relief of symptoms in fifteen of thirty-two asthmatics by the elimination of positively reacting proteins. In a second paper [53] he recommends the use of bacterial vaccines prepared from the stools. He reports one case of colon bacillus allergy and states, furthermore, that in hay-fever and asthma, the normal intestinal

48. Sluder: J. A. M. A. **73**:589 (Sept. 27) 1919.
49. Knapp: Med. Rec. **101**:55, 1921.
50. Kamchorn and Ellis: Am. J. M. Sc. **161**:525, 1921.
51. Hutcheson and Budd: Virginia M. Month. **46**:281, 1919.
52. Gottlieb: J. A. M. A. **75**:814 (Sept. 18) 1920.
53. Gottlieb: J. A. M. A. **74**:931 (April 3) 1920.

flora is often replaced by the predominance of unusual bacteria for these locations, which indicates an intestinal disturbance probably of bacterial origin. This may play a part in the etiology.

Auld [54] in the most recent of several papers on the use of non-specific protein therapy, reports very successful results. He uses injections of Witte's peptone. The patients ought always to be placed in the best possible surroundings and should have specific skin tests before attempting this form of treatment. Cunningham [46] has had good results from a change of climate and believes that for asthmatic children residing in our Atlantic coast cities particularly, the removal inland is indicated when the cause seems to be bacterial.

Sensitization in Eczema.—Fox and Fisher,[55] in sixty cases of eczema in adults, found nineteen giving positive reactions. O'Keefe [56, 57] found that 35 per cent. of 131 bottle fed babies and older children showed sensitization to one or more of the common food proteins. In the order of frequency these foods are egg, milk, potato, wheat and oat. In these cases also, fat or carbohydrate indigestion was more often found than would be the case in an unselected group of children. He suggests that these forms of indigestion make protein sensitization more likely to occur and so produce eczema.

In forty-one exclusively breast fed babies having eczema, he was surprised to find that more than 60 per cent. showed sensitization; 40 per cent. of these being sensitive to egg, 39 per cent. to cow's milk, 5 per cent. to oat, and about 2 per cent. to wheat. None showed a reaction to human milk protein. The conclusion is that human milk must often contain foreign proteins which the babies may absorb in an unbroken form, thus becoming sensitized. The treatment of removing such positively reacting foods from the mothers' diets, together with external remedies, resulted in a cure in seventeen of forty-one treated. Whenever milk or eggs were so limited or omitted, cod liver oil and green vegetables were especially prescribed.

In bottle fed babies those sensitive to casein were fed with whey and cream mixtures. Those sensitive to lactalbumin received milk prepared by boiling and skimming off the coagulated material; for those sensitive to both casein and lactalbumin, the formulae were peptonized or were restricted to the minimum in protein. In nearly 20 per cent. of the seventy cases reported in the first of these two papers there was evidence of heredity.

Sidlick and Knowles,[58] using the intracutaneous method of testing, found that of twenty-five children with eczema, fifteen gave positive

54. Auld: Brit. M. J. **1**:696, 1921.
55. Fox and Fisher: J. A. M. A. **75**:907 (Oct. 2) 1920.
56. O'Keefe: Boston M. & S. J. **183**:569, 1920.
57. O'Keefe: J. A. M. A. **78**:483 (Feb. 18) 1922.
58. Sidlick and Knowles: Am. J. Dis. Child. **23**:316 (April) 1922.

reactions. Of these fifteen, six were either cured or much improved by the removal of the reacting proteins. Of twelve cases with papular eczema, nine reacted to one or more proteins and seven of these patients were either cured or very much improved. We assume that external treatment was also employed. Engman and Wander [59] found skin reactions in 78 per cent. of thirty-six cases of infantile eczema and in every instance where control could be exercised got excellent results from the indicated treatment.

Schloss,[3] in fifty-three cases of infantile eczema, found forty giving cutaneous reactions, thirty-four to egg white which had never been eaten but which nevertheless produced symptoms. Thirty-six gave reactions to cow's milk, and although it was difficult to omit this food at this age, six were fed on an artificial milk and, by the the improvement in their eczema, confirmed the indicated etiology of milk protein. Schloss feels that infantile eczema is also often due to the fat or sugar in the food.

In a second group consisting of twenty-four children more than 16 months of age, ten gave positive reactions. In these the type of eczema was rather definite, the patients showing a dry, scaly skin, with weeping areas occurring only in periods of marked exacerbation. The distribution in these cases usually included the hands, forearms, bends of the elbows, and the popliteal spaces. Six of them reacted to so many proteins that therapeutic confirmation of the relation of any one of them was impossible. The remaining four were greatly improved when the protein indicated was removed.

Schloss' figures for children of all ages would show 65 per cent. giving positive cutaneous (scratch) tests. Sidlick and Knowles tested thirty-five children, using the intracutaneous method, and 68 per cent. reacted. With the scratch method in 131 children O'Keefe had only 35 per cent. positives.

The infantile cases of Schloss and of Engman and Wander gave positive reactions in about 77 per cent. of eighty-nine children. O'Keefe's group of breast fed babies, numbering forty-one, were 60 per cent. positive. Allowing for O'Keefe's uniformly lower results, it would appear that breast fed babies may give positive skin tests as often as the bottle fed.

Sensitization in Other Skin Diseases.—Engman and Wander,[59] in ten cases of urticaria, found positive skin reactions in 79 per cent. In chronic general eczema (distinguished from infantile eczema) 38 per cent. of twenty-one patients gave skin reactions. The percentage of reactions was almost negligible in eleven cases of dermatitis herpetiformis, six of erythema multiforme, four lichen urticarius, two of

59. Engman and Wander: Arch. Dermat. & Syph. **3**:223 (April) 1921.

pemphigus, and three of purpura hemorrhagica. Acne vulgaris was negative in eighteen cases, and two others, which were slightly positive, did not respond to specific treatment. Schloss,[3] in sixty children with urticaria, found only ten giving skin reactions, and only four of these were helped by the indicated treatment. The same negligible results were obtained in angioneuritic edema and erythema multiforme. Three cases of acute dermatitis all proved to be due to pollens.

Spain,[60] investigating the nature of ivy poisoning or dermatitis venenata, concludes that typical vesicular lesions can be produced by alcoholic or chloroform extracts of fresh leaves of *Toxicodendron* radicans applied to the skin surface. Such lesions could not be produced by the intradermal injection of the extract, thus indicating that poisoning is not due to allergic sensitization. The age incidence of susceptibility to this irritant is indicated by the fact that 65 per cent. of persons more than 8 years old are susceptible, whereas no reaction could be produced in eighteen infants.

Allergy, Serum Disease and Dermatitis Venenata.—Coca[25] draws the following comparisons: (*a*) Serum disease differs from other forms of human sensitization in the almost constant period of incubation and the high incidence of susceptibility. (*b*) Dermatitis venenata differs from other forms of human hypersensitiveness in which the skin is affected by the constant and characteristic nature of the lesion. (*c*) The age incidence of natural allergies increases rapidly in the early age periods but probably does not greatly exceed 10 per cent. in any period. (*d*) The age incidence of dermatitis venenata increases greatly from childhood to adult life and reaches a very high percentage—probably 90 per cent. (*e*) The age incidence of serum disease seems not to change during life.

Serum Disease.—Gurd and Roberts[61] report a fatal case resulting from the injection of antitetanic horse serum. Kraus et al.,[62] and Krause[63] recommend the use of bovine serum instead of horse serum as a vehicle for diphtheria, tetanus, or other antitoxins, on the ground that it is less liable to cause serum sickness.

Bouche and Huston,[64] studying the reactions in man to from 0.5 to 2 c.c. of horse serum subcutaneously, conclude that both the local and general reactions vary in different persons. There is usually a vascular or sympathetic reaction at first, followed by a trophic or autonomic reaction, and the manifestations of the two phases are those seen in anaphylactic shock.

60. Spain: J. Immunol. **7**:179, 1922.
61. Gurd and Roberts: Lancet **1**:763, 1920.
62. Kraus et al.: München. med. Wchnschr. **68**:1244, 1921.
63. Krause: Rev. d. Inst. Bact. **2**:1, 1919.
64. Bouche and Huston: Presse méd. **29**:801, 1921.

Davidson [65] finds that the rashes of serum disease differ in relative frequency and in the order of occurrence, the order in either respect being urticarial, morbilliform and circinate. He suggests the possibility of a distinct mechanism for each. The most important symptoms accompanying such rashes are pyrexia, joint pains, edema, adenitis, and increased cardiac dulness.

Cowie and Greenthal [66] found that normal horse serum always protects guinea-pigs against lethal doses of diphtheria toxin if injected in sufficient quantity and question the superior value of serum from immunized horses.

Lewis [67] believes that the rate of absorption of subcutaneously injected serum or protein solutions is so slow that even when the site of the injection is massaged it could not account for the cases of sudden death occasionally reported. By intravenous injection, on the other hand, animal experiments indicate that extremely small amounts of antigenic protein will bring on fatal anaphylactic spasms. It is by the accidental entering of small veins, therefore, that Lewis accounts for these fatalities in human beings. Cook [68] mentions influences increasing or delaying the rate of absorption.

MacRenzie and Leake,[69] in studies on nineteen patients injected with foreign serum, conclude that their results support the antigen-antibody conception of serum disease.

Intestinal Allergy.—The surprising results of skin tests in exclusively breast-fed babies reported by O'Keefe, 60 per cent. of whom showed positive reactions to proteins other than those of human milk, have been mentioned. The sensitizing capacity of human milk thereby suggested is also pointed out by Shannon.[70] In this report the author mentions three cases, one each of urticaria, indigestion, and papular eczema, all being in nursing babies. In each case he was able to demonstrate by the anaphylactic reaction that egg protein had passed into the mothers' milk. All three babies were relieved of symptoms after the mothers had omitted egg from their diets. In one baby the skin test for egg yolk was positive.

Schloss [3] presents experiments showing that the ingestion of foreign protein, both milk and egg, by guinea-pigs causes the development of immune reactions. Furthermore, Grulee and Bonar [71] examined 136 specimens of urine from twenty-five infants selected only in being from 1 to 13 days old. These babies differed from controls in that they

65. Davidson: Glasgow M. J. **92**:20, 1919.
66. Cowie and Greenthal: J. M. Research **41**:261, 1919.
67. Lewis: J. A. M. A. **76**:1342 (May 14) 1921.
68. Cook: J. Immunol. **5**:39, 1920.
69. MacKenzie and Leake: J. Exper. M. **33**:601, 1921.
70. Shannon: Am. J. Dis. Child. **22**:223 (Sept.) 1921.
71. Grulee and Bonar: Am. J. Dis. Child. **21**:89 (Jan.) 1921.

received egg albumin water between feedings instead of plain water. Of the twenty-five test cases, eighteen showed a positive precipitin reaction to egg white in their urines at some time during these thirteen days of life. From seventeen control babies, forty-one urines gave no positive reactions. These results indicate that the intestinal wall of the new-born infant from the fourth to the tenth day, inclusive, is permeable to egg white in quantities sufficient to be determined by the precipitin reaction in the urine. It seems likely that this is not a peculiarity of specific cases but is a general characteristic of this period of life and suggests an explanation of the frequent sensitization to egg and other foreign proteins. In a previous paper,[72] Grulee had determined that egg albumin is usually completely broken down by the digestive processes in infants and children, as indicated by the infrequency with which he had obtained positive precipitin reactions to this substance in the stools.

Zubizarreta[73] believes that the feeding of cow's milk to babies sensitizes them occasionally against cow's lymph and so accounts for the cases sometimes seen of severe disturbances following vaccination. Wells and Osborne[74] isolated four chemically distinct proteins from cow's milk by the use of the anaphylactic reaction in guinea-pigs. These are casein, lactalbumin, lactoglobulin, and an alcohol soluble protein. Lactalbumin and serum globulin appear to be chemically indistinct and produce mutual sensitization in guinea-pigs.

Duke[75] mentions six cases of abdominal pain apparently the result of food allergy. He believes that food allergy is observed more frequently in persons who have had lesions of the gastro-intestinal tract than in normal persons. Zubizarreta[73] believes that if food is not completely "homologized" in the upper intestinal tract it is likely to produce sensitization. He also believes that eggs are more easily digested after being kept for a while, and is in favor of extracts of the stomach or of upper intestinal tissues rich in the ferments of digestion and "homologization" or of peptone or of beef extract given in 0.5 gm. doses one half hour before meals as an anti-anaphylactic.

Schloss[3] states that the usual gastro-intestinal disturbances consist of vomiting and diarrhea; that infants showing these symptoms acutely, together with urticaria and edema, always give a cutaneous reaction to cow's milk protein and their symptoms occur after the ingestion of very small amounts of milk. In another group symptoms are less acute and may not occur until the milk has been taken for several days. These rarely show positive reactions to cow's milk, but

72. Grulee: Am. J. Dis. Child. **20**:15 (July) 1920.
73. Zubizarreta: Semana méd., Buenos Aires **27**:513, 1921.
74. Wells and Osborne: J. Infect. Dis. **29**:200 (Aug.) 1921.
75. Duke: Arch. Int. Med. **28**:151 (Aug.) 1921.

that the conditions may, nevertheless, be caused by protein sensitization is indicated by the good results of feeding boiled or evaporated milk and by the fact that infants suffering from identical symptoms may show positive reactions to milk protein. Immunity to certain foods can be developed by the ingestion of graduated doses. In twenty cases of cyclic vomiting he found only two giving positive skin tests. Blackfan [76] believes that the absolute omission of offending foods may be unnecessary, since some patients can tolerate them in small quantities. A high temperature is, in his experience, apt to prevent these disturbances. He considers desensitization by all means the most satisfactory method of procedure, and feels that in young infants and children this is best done by mouth rather than by subcutaneous injection. Cunningham [46] feels that by the omission of these foods for varying periods sensitization often disappears spontaneously, and for this reason recommends postponing artificial measures of desensitization when possible until it is determined after two or three months that this will not occur. Park [16] mentions an interesting case of food allergy resulting in the spontaneous disappearance of the hypersensitive condition.

Other Conditions Due to Allergy.—Pagniez and Leutand [77] refer to cases of epilepsy apparently due to sensitization, but base their diagnoses on the observed results of ingestion of or contact with the proteins, rather than on the results of skin tests.

Drug Idiosyncrasy.—Cooke [78] states that in fifteen cases of drug reactions a positive history of family hypersensitiveness occurred in twelve. In the remaining three cases the evidences of sensitization were multiple and included such conditions as asthma, urticaria, and hay-fever occurring in the same individual. Occasionally with the antipyretics hyperpyrexia occurs, or cardiac collapse. In virtually all cases there was a marked eosinophilia. Acetylsalicylic acid reactions were the most frequently encountered by this author. Symptoms begin in from fifteen to twenty minutes after the ingestion of 10 grains and may last from eight to thirty-six hours. Positive cutaneous reactions do not occur except in those cases giving a history of urticaria.

Cooke classes the types of drug action as follows: (*a*) Normal action—side action and toxic action. (*b*) Idiosyncrasic action—either exaggerated normal or exaggerated side action, or lessened normal action (tolerance). (*c*) Allergic action—abnormal.

Labbe and Haguenau [79] report a case of antipyrin sensitization, and Peshkin [80] cites one of ipecac idiosyncrasy with asthma.

76. Blackfan: Am. J. M. Sc. **160**:341, 1920.
77. Pagniez and Lieutand: Presse méd. **27**:693, 1920.
78. Cooke: J. A. M. A. **73**:759, 1919.
79. Labbe and Hagenau: Bull. et mém. Soc. méd. d. hôp. de Paris **43**:549, 1921.
80. Peshkin: J. A. M. A. **75**:1133 (Oct. 23) 1920.

Lane [81] reports three cases of susceptibility to procain in dentists, confirming the diagnosis by skin tests, and suggests the possibility of general reactions to this substance.

Stuart and Maynard [82] report an interesting case of hypersensitiveness to arsphenamin following an exfoliative dermatitis which gave a marked intracutaneous skin reaction. They examined in this way ten other cases treated with arsphenamin and sixteen controls. No positive skin tests were found among the controls. Of the other ten cases, seven gave no reaction. Two patients gave positive reactions and had lumbar pain beginning four days after an injection of arsphenamin and lasting four weeks. The third patient exhibited the same lumbar pain following the last injection but gave no skin reaction, possibly because the most recent therapeutic dose had been given as long as nine months previously.

Nonspecific Treatment.—Most of this treatment is given either by mouth or intravenously. Commenting on the use of intravenous treatment, Hanzlik and Karsner [83] studied twenty-nine agents given in this way and concluded that they were distinctly harmful in varying degrees. They are, therefore, opposed to the promiscuous and unwarranted giving of drugs by the intravenous method.

Auld [84] has written several reports on the successful treatment of asthma with Witte's peptone given intravenously. Pagniez and Vallery-Radot [84] believe that "alimentary anaphylaxis" can be avoided by the preliminary injection of peptone. Van Leeuwen and Varekamp [85] tried specific skin tests but concluded that nonspecific injections (they use tuberculin) give better results. Shulman [86] reports good results in the treatment of sixty cases of arthritis, and especially arthritis of gonorrheal origin, by the injection of milk. Snyder and Ramirez,[87] reporting on seventy cases of chronic arthritis, conclude that such patients as have not been relieved by the routine treatment with salicylates, hot packs, baking, and massage, are, as a rule, materially benefited by the intravenous administration of small doses of foreign protein. Such benefit is almost always in the joints of the upper extremities. Patients prefer secondary proteoses to typhoid bacilli because they seem to cause less discomfort. The effects in relieving pain and improving motion seem equally good.

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81. Lane: Arch. Dermat. & Syph. **3**:235 (April) 1921.
82. Stuart and Maynard: Arch. Int. Med. **26**:511 (Oct.) 1920.
83. Hanzlik and Karsner: J. Pharmacol. & Exper. Therap. **14**:379, 1920.
84. Pagniez and Vallery-Radot: Ann. de méd. **8**:303, 1920.
85. Van Leeuwen and Varekamp: Lancet **2**:1366, 1921.
86. Shulman: Med. Rec. **98**:47, 1920.
87. Snyder and Ramirez: Arch. Int. Med. **28**:50 (July) 1921.

Joltrain,[88] Zubizarreta,[73] and Nathan[89] favor treatment by preliminary ingestion of peptone or extracts of certain of the digestive tissues to prevent "alimentary anaphylaxis."

Danysz[90] reports further successes in the treatment of nonfebrile chronic diseases by means of cultures of nonpathogenic intestinal micro-organisms. His most effective preparations seem to contain strains of *Bacillus coli, B. proteus,* streptococcus, staphylococcus, and enterococcus. He differs the proportions for psoriasis, enteritis, asthma, etc. His reports may be compared with those of four other authors already quoted, Turnbull,[12] Larsen, Paddock and Alexander,[13] Cooke[43] and Gottlieb.[53]

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88. Joltrain: Bull. et mém. Soc. méd. d. hôp. de Paris **43**:556, 1921.
89. Nathan: Bull. méd., Par. **34**:59, 1920.
90. Danysz: Bull. méd., Par. **34**:657, 1920.